Age-related changes in neural control of posture

Papegaaij, Selma

AGE-RELATED CHANGES IN NEURAL CONTROL OF POSTURE

S. Papegaaij

The studies described in chapter 2 to 5 of this thesis were conducted at the Center for Human Movement Sciences, part of the University Medical Center Groningen, University of Groningen, the Netherlands. The study described in chapter 6 was conducted at the Jacobs Center on Lifelong Learning and Institutional Development, part of the Jacobs University, Bremen, Germany.

This thesis was financially supported by:

- University Medical Center Groningen
- Graduate School of Medical Sciences
- Gratama Stichting
- Jacobs University
- Fysiotherapie Papegaaij & Tegelaar

Cover design: Nadia Colombo - www.urbanemotions.com
Print: Ipskamp drukkers
ISBN: 978-90-367-8629-4 (book)
ISBN: 978-90-367-8630-0 (E-book)

Paranymphs: A. Kornfeld and U. Schepke

rijksuniversiteit groningen

Age-related changes in neural control of posture

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 20 april 2016 om 12.45 uur

door

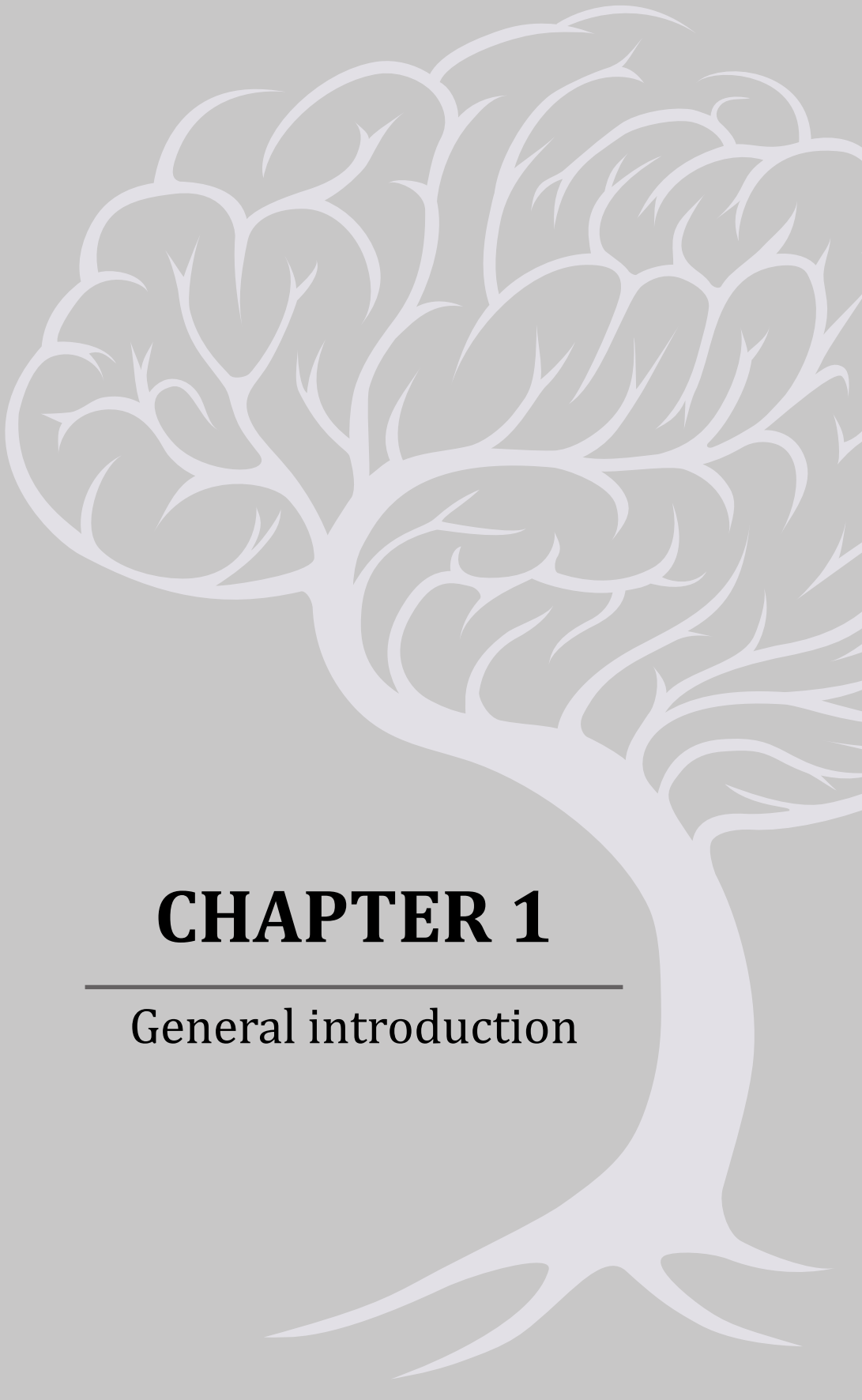
Selma Papegaaij

geboren op 21 augustus 1986
te Kampen

Promotores
Prof. dr. T. Hortobágyi
Prof. dr. E. Otten

Beoordelingscommissie
Prof. dr. J. van Dieën
Prof. dr. T. van Laar
Prof. dr. N. Wenderoth

TABLE OF CONTENTS



CHAPTER 1

General introduction

1. GENERAL INTRODUCTION

Natural aging is associated with adverse changes in various structures and functions, such as declines in muscle strength [1,2], sensory acuity [3-6], cognitive abilities [7], nerve conduction velocity [8], and gray and white matter [9-13]. It is therefore not surprising that postural control, in this thesis defined as the control of upright standing, is compromised in old compared with young adults [14-16]. Although the effects of motor and sensory decline on postural control have been studied extensively, age-related changes in neural control of posture are largely unknown. A better understanding of such changes would help in developing new and improving existing exercise- and drug- based balance interventions.

1.1. Cortical involvement in postural control

Although standing is often considered a static postural task, destabilizing gravitational forces caused by minor deviations from the vertical require corrective joint torques to maintain the upright position [17]. Visual, proprioceptive, and vestibular systems provide means to sense the orientation and movement of the body. The muscular system then generates the corrective joint torques to control center of mass movement. The current thesis focusses on the system linking these sensory and motor aspects of postural control; the central nervous system.

The central nervous system can be divided into spinal, subcortical, and cortical structures. Early work on neural control of posture in decerebrated animals suggested that standing relies mainly on spinal reflexes and subcortical centers [18,19]. However, behavioral studies [20] indicated that cortical lesions do affect postural control [20-23] and that expectation and context can influence postural responses after a perturbation [24]. Imaging studies also revealed that several cortical structures are active during actual or imagined standing [25,26]. Moreover, electro-physiological studies reported that cortical activity precedes predictable postural perturbations [27] and that motor cortical excitability increases during the long latency postural response and during unsupported versus supported standing [28]. In summary, there is ample evidence from a variety of experimental approaches that the cerebral cortex plays a role in postural control.

1.2. Age-related changes in postural control: influence of neural circuits unknown

Aging is associated with increases in magnitude and decreases in complexity of center of pressure movements during upright standing [14,29-31]. This deterioration in postural control can already be detected in middle-aged individuals and increases exponentially after age 60 [14]. The age-related differences in postural control are even more pronounced in conditions of high postural challenge [29,32,33] or when a cognitively demanding task is added [34]. Functional significance of these findings is emphasized by the fact that old adults with greater center of pressure

displacement [35,36] or worse dual-task performance [37-40] exhibit a higher incidence of falls.

At least part of the postural control decrements in old adults can be explained by declines in sensory acuity and muscle performance. Age-related deficits in proprioception (joint position and motion sense) [3], vision [4,41], and vestibular function [5,6,42] are associated with worse postural control [43-46]. Furthermore, fallers compared with non-fallers exhibit lower muscle strength and power [47,48]. Especially muscle power seems to be important, as high-velocity muscle power training is more effective than traditional resistance training in improving postural control in old adults [49,50].

In addition to the sensory and muscular systems, age also affects the central nervous system. For example, quality and quantity of cortical grey and white matter significantly declines with age [9-13]. Until now, the majority of studies have used manual tasks to investigate the effect of these structural changes on how the brain operates during motor performance [51-55]. The emerging picture from these studies is that aging causes a reorganization of cortical control of voluntary movement, with an increase in brain activation and decrease in cortical inhibition. As the neural circuits affected by age-related degeneration are also involved in postural control, it is likely that changes in brain activation and inhibition also occur during standing. However, the functional changes in neural control of posture with age and their relation to postural deficits are not yet known.

1.3. Modulating intracortical inhibition to regulate motor cortical excitability

In the human brain, the major inhibitory neurotransmitter is the amino acid gamma-amino-butyric-acid (GABA) [56]. GABAergic intracortical inhibitory neurons constitute 10-25% of all cortical neurons and play an important role in regulating neural activity levels [57]. Intracortical inhibitory neurons are also involved in motor control, indicated by a reduction in intracortical inhibition when voluntarily contracting a muscle [58-61]. This down-modulation of intracortical inhibition most likely reflects a mechanism to selectively increase the excitability of pyramidal neurons projecting to the spinal motor neurons of the contracted muscle [58,62]. Accordingly, intracortical inhibition is also modulated with contraction intensity [59,61], directionality of movement [63], and movement phase [64]. Although intracortical inhibition also decreases during postural contractions in standing [65], and the excitability of the corticospinal pathway increases with postural task difficulty [66-69], the influence of postural task difficulty on cortical measures as intracortical inhibition is still unclear.

1.4. Thesis aim and outline

The aim of this thesis is to determine the age-related changes in neural control of posture, as quantified by measures of motor cortical excitability and brain activation, and how such changes affect body sway during standing. Chapter 2 elaborates on the current knowledge of structur-

al and functional changes with aging in the central nervous system and their relation to motor performance. This chapter also identifies the knowledge gaps of which some will be addressed in the remainder of the thesis. Chapters 3 to 5 describe a series of experiments designed to systematically investigate modulation of motor cortical excitability with postural task difficulty in young and old adults. Motor cortical excitability was quantified by intracortical inhibition and facilitation as assessed in the soleus and tibialis anterior muscles using transcranial magnetic stimulation (TMS). Although TMS has the advantage that measurements can be performed during standing, it is limited to the motor cortex and cannot measure neuronal activation. Therefore, we also conducted a functional magnetic resonance imaging (fMRI) study (chapter 6). For this study, we developed a system to simulate standing in the MRI scanner. The main question that this chapter addresses is whether the decreased ability of old adults to perform a motor-cognitive dual-task is related to the age-related increase in brain activation. Finally, chapter 7 will provide a general discussion of the findings reported in this thesis.

REFERENCES

1. Beenakker KG, Ling CH, Meskers CG, de Craen AJ, Stijnen T, Westendorp RG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Res Rev 2010 Oct;9(4):431-436.

2. Charlier R, Mertens E, Lefevre J, Thomis M. Muscle mass and muscle function over the adult life span: a cross-sectional study in Flemish adults. Arch Gerontol Geriatr 2015 Sep-Oct;61(2):161-167.

3. Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP. Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. Neurosci Biobehav Rev 2009 Mar;33(3):271-278.

4. Schumm LP, McClintock M, Williams S, Leitsch S, Lundstrom J, Hummel T, et al. Assessment of sensory function in the National Social Life, Health, and Aging Project. J Gerontol B Psychol Sci Soc Sci 2009 Nov;64 Suppl 1:i76-85.

5. Li C, Layman AJ, Carey JP, Agrawal Y. Epidemiology of vestibular evoked myogenic potentials: Data from the Baltimore Longitudinal Study of Aging. Clin Neurophysiol 2015 Jan 24.

6. Hsieh LC, Lin HC, Lee GS. Aging of vestibular function evaluated using correlational vestibular autorotation test. Clin Interv Aging 2014 Sep 3;9:1463-1469.

7. Katz MJ, Lipton RB, Hall CB, Zimmerman ME, Sanders AE, Verghese J, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Dis Assoc Disord 2012 Oct-Dec;26(4):335-343.

8. Verdu E, Ceballos D, Vilches JJ, Navarro X. Influence of aging on peripheral nerve function and regeneration. J Peripher Nerv Syst 2000 Dec;5(4):191-208.

9. Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am J Neuroradiol 2002 Sep;23(8):1327-1333.

10. Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and

hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol Aging 2004 Mar;25(3):377-396.

11. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, et al. Thinning of the cerebral cortex in aging. Cereb Cortex 2004 Jul;14(7):721-730.

12. Zhao T, Cao M, Niu H, Zuo XN, Evans A, He Y, et al. Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. Hum Brain Mapp 2015 Oct;36(10):3777-3792.

13. Yeatman JD, Wandell BA, Mezer AA. Lifespan maturation and degeneration of human brain white matter. Nat Commun 2014 Sep 17;5:4932.

14. Era P, Sainio P, Koskinen S, Haavisto P, Vaara M, Aromaa A. Postural balance in a random sample of 7,979 subjects aged 30 years and over. Gerontology 2006;52(4):204-213.

15. Era P, Heikkinen E, Gause-Nilsson I, Schroll M. Postural balance in elderly people: changes over a five-year follow-up and its predictive value for survival. Aging Clin Exp Res 2002 Jun;14(3 Suppl):37-46.

16. Abrahamova D, Hlavacka F. Age-related changes of human balance during quiet stance. Physiol Res 2008;57(6):957-964.

17. Peterka RJ. Sensorimotor integration in human postural control. J Neurophysiol 2002 Sep;88(3):1097-1118.

18. Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 1910 Apr 26;40(1-2):28-121.

19. Magnus R. Some results of studies in the physiology of posture. Lancet 1926;2:585-588.

20. Sackley CM. Falls, sway, and symmetry of weight-bearing after stroke. Int Disabil Stud 1991 Jan-Mar;13(1):1-4.

21. Geurts AC, de Haart M, van Nes IJ, Duysens J. A review of standing balance recovery from stroke. Gait Posture 2005;22(3):267-281.

22. Dickstein R, Nissan M, Pillar T, Scheer D. Foot-ground pressure pattern of standing hemiplegic patients. Major characteristics and patterns of improvement. Phys Ther 1984 Jan;64(1):19-23.

23. Yanohara R, Teranishi T, Tomita Y, Tanino G, Ueno Y, Sonoda S. Recovery process of standing postural control in hemiplegia after stroke. J Phys Ther Sci 2014 Nov;26(11):1761-1765.

24. Jacobs JV, Horak FB. Cortical control of postural responses. J Neural Transm 2007;114(10):1339-1348.

25. Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: A PET study. Hum Brain Mapp 2003;19(1):47-62.

26. Taube W, Mouthon M, Leukel C, Hoogewoud HM, Annoni JM, Keller M. Brain activity during observation and motor imagery of different balance tasks: an fMRI study. Cortex 2015 Mar;64:102-114.

27. Jacobs JV, Fujiwara K, Tomita H, Furune N, Kunita K, Horak FB. Changes in the activity of the cerebral cortex relate to postural response modification when warned of a perturbation. Clin Neurophysiol 2008 Jun;119(6):1431-1442.

28. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of human standing. Acta Physiol (Oxf) 2009 Mar;195(3):385-395.

29. Zhou J, Manor B, Liu D, Hu K, Zhang J, Fang J. The complexity of standing postural control in older adults: a modified detrended fluctuation analysis based upon the empirical mode decomposition algorithm. PLoS One 2013 May 1;8(5):e62585.

30. Costa M, Priplata AA, Lipsitz LA, Wu Z, Huang NE, Goldberger AL, et al. Noise and poise: Enhancement of postural complexity in the elderly with a stochastic-resonance-based therapy. Europhys Lett 2007 Mar;77:68008.

31. Ko JH, Newell KM. Aging and the complexity of center of pressure in static and dynamic postural tasks. Neurosci Lett 2015 Nov 5;610:104-109.

32. Amiridis IG, Hatzitaki V, Arabatzi F. Age-induced modifications of static postural control in humans. Neurosci Lett 2003 Oct 30;350(3):137-140.

33. Whipple R, Wolfson L, Derby C, Singh D, Tobin J. Altered sensory function and balance in older persons. J Gerontol 1993 Sep;48 Spec No:71-76.

34. Ruffieux J, Keller M, Lauber B, Taube W. Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan. Sports Med 2015 Aug 8.

35. Muir JW, Kiel DP, Hannan M, Magaziner J, Rubin CT. Dynamic parameters of balance which correlate to elderly persons with a history of falls. PLoS One 2013 Aug 5;8(8):e70566.

36. Mignardot JB, Beauchet O, Annweiler C, Cornu C, Deschamps T. Postural sway, falls, and cognitive status: a cross-sectional study among older adults. J Alzheimers Dis 2014;41(2):431-439.

37. Beauchet O, Annweiler C, Dubost V, Allali G, Kressig RW, Bridenbaugh S, et al. Stops walking when talking: a predictor of falls in older adults? Eur J Neurol 2009 Jul;16(7):786-795.

38. Beauchet O, Annweiler C, Allali G, Berrut G, Herrmann FR, Dubost V. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? J Am Geriatr Soc 2008 Jul;56(7):1265-1269.

39. Walshe EA, Patterson MR, Commins S, Roche RA. Dual-task and electrophysiological markers of executive cognitive processing in older adult gait and fall-risk. Front Hum Neurosci 2015 Apr 17;9:200.

40. Wang X, Pi Y, Chen P, Liu Y, Wang R, Chan C. Cognitive motor interference for preventing falls in older adults: a systematic review and meta-analysis of randomised controlled trials. Age Ageing 2015 Mar;44(2):205-212.

41. Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004 Apr;122(4):477-485.

42. Baloh RW, Jacobson KM, Socotch TM. The effect of aging on visual-vestibuloocular responses. Exp Brain Res 1993;95(3):509-516.

43. McChesney JW, Woollacott MH. The effect of age-related declines in proprioception and total knee replacement on postural control. J Gerontol A Biol Sci Med Sci 2000 Nov;55(11):M658-66.

44. Aartolahti E, Hakkinen A, Lonnroos E, Kautiainen H, Sulkava R, Hartikainen S. Relationship between functional vision and balance and mobility performance in community-dwelling older adults. Aging Clin Exp Res 2013 Oct;25(5):545-552.

45. Lord SR. Visual risk factors for falls in older people. Age Ageing 2006 Sep;35 Suppl 2:ii42-ii45.

46. Serrador JM, Lipsitz LA, Gopalakrishnan GS, Black FO, Wood SJ. Loss of otolith function with age is associated with increased postural sway measures. Neurosci Lett 2009 Nov 6;465(1):10-15.

47. Perry MC, Carville SF, Smith IC, Rutherford OM, Newham DJ. Strength, power output and symmetry of leg

muscles: effect of age and history of falling. Eur J Appl Physiol 2007 Jul;100(5):553-561.

48. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2004 Jul;52(7):1121-1129.

49. Granacher U, Muehlbauer T, Zahner L, Gollhofer A, Kressig RW. Comparison of traditional and recent approaches in the promotion of balance and strength in older adults. Sports Med 2011 May 1;41(5):377-400.

50. Orr R, de Vos NJ, Singh NA, Ross DA, Stavrinos TM, Fiatarone-Singh MA. Power training improves balance in healthy older adults. J Gerontol A Biol Sci Med Sci 2006 Jan;61(1):78-85.

51. Fling BW, Seidler RD. Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. Cereb Cortex 2012 Nov;22(11):2643-2652.

52. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008 Jan 2;28(1):91-99.

53. Ward NS, Swayne OB, Newton JM. Age-dependent changes in the neural correlates of force modulation: an fMRI study. Neurobiol Aging 2008 Sep;29(9):1434-1446.

54. Marneweck M, Loftus A, Hammond G. Short-interval intracortical inhibition and manual dexterity in healthy aging. Neurosci Res 2011 Aug;70(4):408-414.

55. Heise KF, Zimerman M, Hoppe J, Gerloff C, Wegscheider K, Hummel FC. The Aging Motor System as a Model for Plastic Changes of GABA-Mediated Intracortical Inhibition and Their Behavioral Relevance. J Neurosci 2013 May 22;33(21):9039-9049.

56. Luhmann HJ, Kirischuk S, Sinning A, Kilb W. Early GABAergic circuitry in the cerebral cortex. Curr Opin Neurobiol 2014 Jun;26:72-78.

57. Le Magueresse C, Monyer H. GABAergic interneurons shape the functional maturation of the cortex. Neuron 2013 Feb 6;77(3):388-405.

58. Ridding MC, Taylor JL, Rothwell JC. The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. J Physiol 1995 Sep 1;487 (Pt 2)(Pt 2):541-548.

59. Rantalainen T, Weier A, Leung M, Brandner C, Spittle M, Kidgell D. Short-interval intracortical inhibition is not affected by varying visual feedback in an isometric task in biceps brachii muscle. Front Hum Neurosci 2013 Mar 8;7:68.

60. Sharples SA, Kalmar JM. Modulation of cortical excitability and interhemispheric inhibition prior to rhythmic unimanual contractions. J Neurosci Methods 2012 Sep 30;210(2):178-186.

61. Ortu E, Deriu F, Suppa A, Tolu E, Rothwell JC. Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. J Physiol 2008 Nov 1;586(Pt 21):5147-5159.

62. Zoghi M, Pearce SL, Nordstrom MA. Differential modulation of intracortical inhibition in human motor cortex during selective activation of an intrinsic hand muscle. J Physiol 2003 Aug 1;550(Pt 3):933-946.

63. Howatson G, Taylor MB, Rider P, Motawar BR, McNally MP, Solnik S, et al. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. Eur J Neurosci 2011 Mar;33(5):978-990.

64. Sidhu SK, Cresswell AG, Carroll TJ. Short-interval intracortical inhibition in knee extensors during locomotor cycling. Acta Physiol (Oxf) 2013 Jan;207(1):194-201.

65. Soto O, Valls-Sole J, Shanahan P, Rothwell J. Reduction of intracortical inhibition in soleus muscle during

postural activity. J Neurophysiol 2006 Oct;96(4):1711-1717.

66. Ackermann H, Scholz E, Koehler W, Dichgans J. Influence of posture and voluntary background contraction upon compound muscle action potentials from anterior tibial and soleus muscle following transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991 Feb;81(1):71-80.

67. Nakazawa K, Kawashima N, Obata H, Yamanaka K, Nozaki D, Akai M. Facilitation of both stretch reflex and corticospinal pathways of the tibialis anterior muscle during standing in humans. Neurosci Lett 2003 Feb 20;338(1):53-56.

68. Obata H, Sekiguchi H, Nakazawa K, Ohtsuki T. Enhanced excitability of the corticospinal pathway of the ankle extensor and flexor muscles during standing in humans. Exp Brain Res 2009 Aug;197(3):207-213.

69. Solopova IA, Kazennikov OV, Deniskina NB, Levik YS, Ivanenko YP. Postural instability enhances motor responses to transcranial magnetic stimulation in humans. Neurosci Lett 2003 Jan 30;337(1):25-28.

CHAPTER 2

Aging causes a reorganization of cortical and spinal control of posture

S. Papegaaij

W. Taube

S. Baudry

E. Otten

T. Hortobágyi

Frontiers in Aging Neuroscience 2014 March 3;6:28.

.

ABSTRACT

Classical studies in animal preparations suggest a strong role for spinal control of posture. In humans it is now established that the cerebral cortex contributes to postural control of unperturbed and perturbed standing. The age-related degeneration and accompanying functional changes in the brain, reported so far mainly in conjunction with simple manual motor tasks, may also affect the mechanisms that control complex motor tasks involving posture. This review outlines the age-related structural and functional changes at spinal and cortical levels and provides a mechanistic analysis of how such changes may be linked to the behaviorally manifest postural deficits in old adults. The emerging picture is that the age-related reorganization in motor control during voluntary tasks, characterized by differential modulation of spinal reflexes, greater cortical activation and cortical disinhibition, is also present during postural tasks. We discuss the possibility that this reorganization underlies the increased coactivation and dual task interference reported in elderly. Finally, we propose a model for future studies to unravel the structure-function-behavior relations in postural control and aging.

1. INTRODUCTION

The aging neuromotor system endures structural and functional changes that induce adjustments in motor output. Figure 1 depicts the different domains of age-related changes in the neuromotor system controlling postural and manual tasks. Structural changes refer to a quantitative and qualitative degeneration of gray and white matter and peripheral nerves, whereas functional changes refer to modifications in how these structures operate during a motor task. Functional changes can either be negative (a functional deterioration) or positive (a compensation for the functional deterioration) [1]. The extent to which compensation manages to restore function will eventually determine the magnitude of behavioral changes, measured as the change in performance in a motor task.

The preponderance of studies examining the cascade of structure-function-behavior in the aging neuromotor system has used simple manual tasks as a model [2-6]. Although tasks such as index finger abduction are relevant to study how aging affects motor control under specific experimental conditions, a simple extension of those findings to complex motor tasks such as those associated with activities of daily living that involve the trunk and the lower extremities would be ecologically invalid. Therefore, the purpose of the present paper is to review the age-related

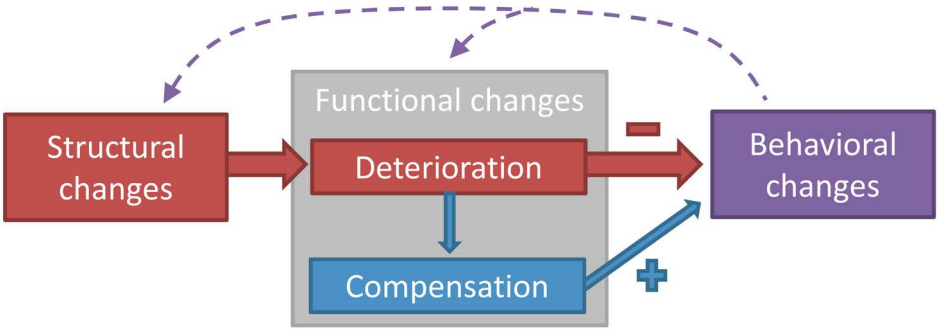


Figure 1 | A classification model of the different domains of age-related changes in the neuromotor system controlling postural and manual tasks. Three domains can be distinguished: structural changes, functional changes, and behavioral changes. Structural changes refer to the degeneration of brain or nerve structures with aging, whereas functional changes refer to the age-related modification in how these structures operate in the act of motor control. Behavioral changes denote the changes in performance on the motor task, which can be both a postural or a manual task. Functional changes can be divided into deterioration (as a direct result of the structural changes) and compensation (changes in function to counteract the deterioration). Structural degeneration causes functional deterioration [56], which triggers the need for functional compensation [59]. Functional deterioration has a negative impact on performance [97], whereas functional compensation has a positive impact [59]. The dashed arrows acknowledge the influence that acute or chronic behavioral changes, i.e., intervention or differences in lifestyle, have on structure and function of the neuromotor system [61,136,144]. The model can be used in future studies to systematically examine the structure-function-behavior link in the aging neuromotor system and could also be applied to other fields of research.

structural and functional changes of the neuromotor system on spinal and cortical level and examine whether these changes are linked to the declines in postural control. Subcortical structures also play a role in postural control [7-9], and age-related changes in subcortical white matter integrity, grey matter volume and striatal dopaminergic denervation have been shown to affect postural performance. [10-12]. Nonetheless, due to a paucity of data on age-related changes in subcortical control of posture, we limited the present review to spinal and cortical mechanisms of postural control.

The concept of postural control can be viewed in a broader perspective, however, for this review we define postural control as the control of upright standing in various conditions. Postural control can be distinguished according to feedback and feedforward control. Feedback control is an ongoing loop of acquisition and integration of sensory information that becomes online updated and corrects posture accordingly during unperturbed and perturbed standing. Feedforward control is an anticipation of potential disturbances and it occurs in anticipatory postural adjustments before a voluntary movement [13], in context-dependent adaptations of postural responses to perturbations [14], and in normal standing [15,16]. As during postural control feedforward and feedback mechanisms are working simultaneously and cooperatively, it is often impossible to divide the literature according to this distinction. However, where possible, contributions of the two control mechanisms will be mentioned.

First we review evidence suggesting a role for the frontal, parietal, and motor cortices in the control of standing in healthy young and old adults. Next, we provide an analytical review on how structural and functional changes in the aging neuromotor system mediate behavioral changes in general. The main analysis then focuses on the age-related changes in the structure-function relationship with respect to posture. The last section summarizes evidence for the plasticity in the mechanisms that mediate adaptations to balance training with the goal to slow if not halt the age-related decline in postural control.

2. CORTICAL CONTROL OF POSTURE

Although classical experiments suggested that the neural control of posture in mammals and primates predominantly relied on spinal reflexes [17], recent studies suggest the involvement and importance of cortical areas in the control of posture during upright standing [18,19]. Behavioral observations in healthy adults, data from patients with cortical lesions, and studies using electro-physiological methods and brain imaging all suggest that postural control involves cortical structures, demonstrating how age-related structural and functional changes in the cortex affect postural control.

Behavioral experiments demonstrate that as soon as subjects receive information about the magnitude of an oncoming postural disturbance, healthy subjects scale and adapt their postural responses according to this information. When subjects receive false cues about a postural

disturbance and subsequently over- or underestimate the actual size of the disturbance, the short latency EMG and center of pressure responses are also, respectively, overscaled and undersized [14]. It may be assumed that these complex feedforward adaptations of postural responses are dependent on the cerebral cortex. In addition, when cognitive demands increase so that the cortical network is charged with the processing of extra workload like in dual- or multitasks, postural performance, quantified by center of pressure measures, decreases (see section Age-Related Reorganization of Postural Control). Impairments in executive functions such as attention, mental calculation, orientation, and memory interfere with balance control, providing additonal evidence for the involvement of cortical circuits in postural control [18].

Further evidence to support the importance of cortical structures for the control of posture comes from experiments conducted in patients. Humans and animals with lesions in the sensorimotor cortex and parieto-temporal junction demonstrate abnormal postural control in perturbed and unperturbed standing, like increased body sway, delayed and reduced muscle responses, and absent hopping and placing reactions [20-23]. In addition, balance control, as quantified by the Berg Balance Scale and incidence of falls, correlates with attention deficits in community dwelling cerebral stroke patients [24].

Using electroencephalography (EEG), Jacobs and coworkers [25] demonstrated that both the activity of the cerebral cortex and the postural reactions adapted in response to cues given prior to rapid horizontal platform perturbations, suggesting that cortical structures are involved in planning postural responses. Similarly, cortical activity was assumed to play a role in preventing falls during voluntary body sway movements as bursts of gamma activity recorded by EEG from frontal and parietal cortical areas were observed to precede the initiation of compensatory postural movements when balance was in danger [26].

Experiments with transcranial magnetic stimulation (TMS) confirm the involvement of the primary motor cortex when a threat to balance is present. In this respect, Taube et al. [27] reported increased excitability of the primary motor cortex at the time of the long latency response (LLR) in the soleus muscle after anterior-posterior perturbation. As no effect was seen at the time of the short latency response (SLR) and medium latency response (MLR), it was proposed that the motor cortex becomes involved after approximately 90-100 ms. However, even in unperturbed quiet standing, motor cortical excitability was higher compared to standing while being lightly supported by a board in front of the body [28]. Similarly, short-interval intracortical inhibition (SICI) was comparable in voluntary contractions and upright stance [29]. Thus, these latter two studies suggest that the primary motor cortex is involved in controlling undisturbed upright stance.

Imaging studies confirm and extend behavioral, EEG, and TMS data concerning the cortical involvement in postural control. A positron emission tomography study revealed increased cortical activity involving the premotor cortex when subjects were asked to imagine themselves

standing while they were lying in the scanner [30]. Using functional magnetic resonance imaging (fMRI), Zwergal and co-workers [31] recorded brain activity in healthy adults age 24-78 when imagining lying, standing and walking. The basic locomotor and postural networks that were activated consisted of the prefrontal cortex, the basal ganglia, the brainstem, and cerebellar centers. Focusing on the sensory aspects that are important for postural control, Goble et al. [32] recorded brain activation with fMRI while the dorsal side of the foot was mechanically vibrated at 80 Hz, a stimulus known to excite Ia afferents as part of the proprioception system. There was a positive correlation between the magnitude of activity in parietal, frontal, and insular cortical areas, as well as structures within the basal ganglia in response to vibration, and balance performance during upright stance with eyes closed.

Altogether there is convincing evidence through a variety of approaches that in addition to spinal and subcortical circuits, supraspinal structures like the frontal, parietal and motor cortices are involved in the control of upright standing. Because age affects the very same structures, it is reasonable to expect an age-related reorganization in the neural control of posture.

3. AGE-RELATED CHANGES IN NEURAL STRUCTURES INVOLVED IN POSTURAL CONTROL

Age induces degeneration of numerous structures in the musculoskeletal, cardiovascular, and nervous system. These structural changes affect functionality of the different systems, forcing a reorganization of the mechanisms that control this functionality so that impairments in motor behavior are minimal (Figure 1). Because the previous section established that postural control involves spinal and cortical structures, this section will outline the structural changes with aging in the nervous system on both levels, in an effort to understand the basis of the reorganization in postural control with aging.

3.1. Age-related structural changes on the peripheral and spinal level

Structural changes in spinal circuits affect their functionality and complicate motor control. We refer to spinal level when sensory and motor neurons and interneurons located in the spinal cord are involved. Morphological studies in aged rodents showed a loss of 38% in myelinated and 46% in unmyelinated fibers of peripheral nerves in the leg , with a decrease in fiber density and myelin thickness and an increase of infolded or outfolded myelin loops [33,34]. Similarly in humans, there is 37% and 38% decline, respectively, in unmyelinated and myelinated fiber density [35]. The decrease in myelinated fiber numbers and the degeneration of the remaining myelin sheaths are, at least in part, responsible for the 8-18 % age-related decrease in nerve conduction velocity [33]. Since there is no difference in soleus M-wave latency between young and old adults (5.19 vs 5.18 ms) despite a delayed H-reflex (29.85 vs 33.24 ms), it seems that afferent axons and/or synapses are more affected [36]. Also, there is an age-related reduction in the number of muscle

spindles, an important sensory source for postural control [37]. Degeneration of efferent pathways is evident in the tibialis anterior, with a decline of 39% in estimated motor unit number in old (66 years) compared with young (27 years) men along with an even greater decline of 61% in very old (82 years) compared with young men [38]. Isometric muscle strength did not decrease beyond age 80, probably because of collateral reinnervation of muscle fibers, increasing the size of the remaining motor units [38-40].

3.2. Age-related structural changes on the cortical level

In addition to the morphological alteration of spinal neurons and motor units, cortical neurons also exhibit structural changes that contribute to the evolving dysfunction of the aging neuromotor system. Structural changes on cortical level are related to gray and white matter volume and white matter integrity, parameters most often measured by specific sequences of magnetic resonance imaging. Gray matter consists of neuronal cell bodies, neuropil, specific glial cells, and capillaries. In general, gray matter volume decreases 4-16% with age in a wide range of cortical areas [41-45]. The shrinkage occurs in association areas located in the prefrontal and the inferior parietal cortices, as well as unimodal sensory and motor areas [43-46]. The physiological changes underlying this cortical thinning are not yet fully understood. However, it is thought that in healthy aging reduced neuronal complexity (neuronal size, synaptic density, presynaptic terminals, etc.) has a greater contribution to cortical thinning than an actual reduction in cell numbers [45,47]. The functional relevance of the reduction in gray matter volume for motor performance is evidenced by its correlation with performance declines in mirror drawing [48] and reaching [49].

White brain matter comprises predominantly glial cells and myelinated axons that connect regions of the cerebrum and the lower brain centers. Aging has a negative effect on white matter quantity, although this volumetric decline starts later and it accelerates faster than the shrinkage of gray matter [42]. White matter tissue integrity, measured by fractional anisotropy and diffusivity, declines linearly with age at a rate of about 2.5% per decade [50,51]. Brain structure–behavior relationships have been difficult to establish using white matter volumetric measures but have been regularly observed with white matter integrity measures [50]. The decrease in white matter integrity, primarily in the corpus callosum, that constitutes the largest white matter mass in the healthy human brain [52,53], has been associated with a slowing of motor performance on interhemispheric transfer tasks like alternating finger tapping [54]. Also central processing speed, examined by choice reaction tasks, correlates with white matter integrity in old adults [55].

4. AGE-RELATED FUNCTIONAL CHANGES

The structural degeneration causes changes in the function of the affected nerves and neural circuits. These functional changes can either be a deterioration of function as a direct result of

the structural changes, or a compensation for this deterioration (Figure 1). When compensating for functional decline, the neuromotor control system reorganizes and changes the contribution of different subsystems. We note that a compensation to improve performance in one task can be maladaptive for a different task. Because of the scarcity of data directly addressing the functional deterioration and compensation that occurs with aging in postural tasks, we review the next best data, and shed light on the reorganization of the neuromotor system during voluntary motor control in old adults. This will be interpolated to postural control in the following section.

4.1. Age-related functional changes on the peripheral and spinal level

The age-related structural changes in the peripheral nervous system cause deterioration in peripheral nerve function, quantified by reduced nerve conduction velocity and response amplitude. Linear regression analysis on data from a group of 3969 healthy subjects between the ages of 20 and 95 years old showed that age explained 3-9% of the variance in nerve conduction velocity and 7-16% of the variance in sensory and motor response amplitude [56]. Also the joint position sense in the ankle deteriorates with age with about 3% per year between ages 20 and 80 years, probably as a consequence of the degeneration of muscle spindles [57].

Possibly related to the deterioration in peripheral nerve function, aging seems to cause reorganization in the relative contribution of supraspinal and spinal inputs to the gain regulation of isometric force. To produce a higher isometric plantar flexion force, young adults down regulate their presynaptic inhibition, allowing for an intensified excitatory afferent input. In contrast, old adults show less modulation of presynaptic inhibition, despite their ability to modulate the force [58]. This suggests that during a voluntary contraction of a leg muscle, old adults rely less on spinal mechanisms (modulation of presynaptic inhibition) and more on supraspinal mechanisms (descending drive) to increase force. It should be noted however, that postsynaptic mechanisms (e.g. recurrent inhibition, Ib inhibition) might have influenced the results.

4.2. Age-related functional changes on the cortical level

Because of the high complexity of brain compared to peripheral nerve function, simple deterioration in brain function is harder to define. However, fMRI and TMS studies have shown many age-related changes in activation and inhibition patterns during voluntary motor control, again demonstrating reorganization.

Right hand movements are mainly controlled by the left hemisphere, because of the crossover of pyramidal cells to the contralateral side in the medulla oblongata. When healthy young individuals perform a motor task with one hand, brain areas other than the motor network controlling the active hand become also somewhat activated. However, when old adults perform motor tasks with one hand, several brain areas become more strongly activated, including the M1 ipsilateral to the moving hand [4,59-61]. This increased activation was suggested to be the

result of degeneration of the corpus callosum, which generally has a net inhibitory effect on the ipsilateral motor cortex [62]. However, Fling and Seidler [3] found that interhemispheric inhibition is negatively instead of positively correlated with corpus callosum integrity in old adults. Moreover, they found greater interhemispheric facilitation and less interhemispheric inhibition in old compared to young adults. These results suggest a shift from interhemispheric inhibition to excitation in old adults. Most importantly, the decreased interhemispheric inhibition correlated with better motor performance, suggesting that the decreased interhemispheric inhibition served a compensatory purpose for other structural declines. This is in agreement with Mattay et al. [59], who found longer reaction times in old adults who did not show increased activation in the ipsilateral M1 compared with those who did show increased activation. In contrast, Langan et al. [60] and McGregor et al. [61] found that increased ipsilateral M1 activation was associated with longer reaction times in old adults. Hence, increased ipsilateral M1 activation may also be counter-productive and a reflection of non-selective recruitment or de-differentiation. Overall, these studies point to the importance of correlating anatomical and activity related changes in brain structure with motor performance, to be able to understand the functional meaning of the observed cortical changes.

The greater activation in the aging brain during motor tasks is not limited to the ipsilateral M1 and is present in other brain areas, including contralateral M1, prefrontal and premotor areas [4,59,63]. As most studies agree that increased activation in these regions is associated with better motor task performance in old adults, it seems that the greater activation compensates for structural degradation [2,59,64] and signifies the allocation of greater neural resources to execute a motor task. Evidence supporting this hypothesis comes from a study showing a positive association between activity of certain brain areas and handgrip force in healthy young adults [65]. This increase in activation when an increase in force is required was less in old adults in the M1, primary sensory cortex (S1), dorsolateral premotor cortex, and anterior cingulate sulcus, but was higher in the ventrolateral premotor cortex. These results have been replicated in a different cohort [66], and suggest that at least in this task the ventrolateral premotor cortex is compensating for the lack of activation increase in other areas.

One issue with the above-mentioned fMRI studies is that the interpretation of BOLD (blood-oxygen-level dependence) responses is somewhat limited, as it cannot distinguish between inhibition and excitation [67]. For this purpose, TMS techniques can be used to investigate the excitability of different inhibitory and excitatory circuits within the motor cortical areas. In general, it seems that cortical inhibitory circuits are less active in old compared with young adults. In addition to the already mentioned decrease in interhemispheric inhibition, also shorter silent periods, reduced short-interval intracortical inhibition (SICI) and reduced cortical reciprocal inhibition have been associated with aging [5,68-71]. Table 1 summarizes the age-related changes in cortical inhibitory circuits.

Table 1 | Age-related changes in cortical inhibitory circuits.

Reference	Muscles	N	Age	Motor tasks	IHI		cSP	cSP/MEP	SICI	CRI	Correlation MP
					Type	Aging					
Sale and Semmler [69]	FDI	y: 10	y: 27±1	(a) 5% MVC			(a) ↓	(a) ↓			only weak correlations
		o: 10	o: 68±2								
Oliviero et al. [68]	FDI	y: 20	y: 26±4	(r) rest			(a) ↓	(a) =	(r) =		
		o: 22	o: 71±6	(a) 50% MVC							
Talelli et al. [66]	FDI	30	19-78	(a) 15-20% MVC	IHI10	(a) =					
					IHI40	(a) ↓					
Marneweck et al. [71]	FDI	y: 25	y: 18-29	(r) rest					(r) ↓		no SICI visible: MP ↓
		o: 24	o: 59-88								
McGregor et al. [61]	FDI	y: 15	y: 18-37	(a) 40-50% MVC	iSP	(a) ↓					trend IHI ↓ MP ↓
		o: 30	o: 60-85								
Smith et al. [76]	FDI	y: 15	y: 20±2	(r) rest					(r) =		
		o: 15	o: 66±4								
Fling and Seidler [51]	FDI	y: 21	y: 22±3	(a) 20% MVC	iSP	(a)↓/=					IHI ↑ MP ↓
		o: 18	o: 67±5								
Heise et al. [6]	FDI	64	20-88	(r) rest					(r) ↓		SICI rest ↓ MP ↓
				(a) preparation SRT					(a) modulation ↓		SICI modulation ↓ MP ↓
Rogasch et al. [77]	APB	y: 14	y: 21±2	(r) rest					(r) =		
		o: 14	o: 68±6								
Cirillo et al. [78]	APB	y: 12	y: 22±2	(r) rest					(r) =		
		o: 14	o: 67±4								

Table 1 | Continued.

Hinder et al. [146]	APB	y: 10	y: 26±3	(a1) tonic	IHI10	(a1) =					
		o: 10	o: 66±4	(a2) ballistic		(a2) =					
Petitjean and Ko [147]	APB	y: 20	y: 28±7	(a) active	iSP	(a) ↓					
		o: 20	o: 58±7								
Kossev et al. [75]	ECR/FCR	y: 10	y: 29±5	(r) rest					(r) ↑		
		o: 10	o: 56±5								
Hortobágyi et al. [111]	ECR	y: 6	y: 27±4	(r) rest						↓	
		o: 6	o: 73±6								
Fujiyama et al. [5]	ECR	y: 15	y: 18-29	(a1) contralateral ISO			(a1) =				
		o: 15	o: 58-84	(a2) contralateral nonISO			(a2) ↓	(a2) ↓			SP ↓ MP ↓
				(a3) ipsilateral ISO			(a3) =				
				(a4) ipsilateral nonISO			(a4) =				
McGinley et al. [74]	FCR	y: 21	y: 21 ± 1	(r) rest			(a)↑		(r) ↑		
		o: 9	o: 71 ± 2	(a) 15% MVC					(a) =		
Hunter et al. [148]	BIC	y: 17	y: 26 ± 4	(a) 100% MVC			(a) =				
		o: 7	o: 73 ± 3								
Eisen et al. [149]	EDC	y: 23	y: 33 ± 7	(a) active			(a) ↓				
		o: 15	o: 67 ± 9								
Lo and Fook-Chong [150]	AH	30	23-80	(a) 100% MVC	iSP	(a) =	(a) =				
Stevens-Lapsley et al. [79]	VL	y: 20	y: 25 ± 2	(r) rest					(r) =		
		o: 20	o: 58 ± 6								

Arrows indicate direction of change of cortical inhibition in old compared to young adults. Key: N, number of subjects; IHI, interhemispheric inhibition; cSP & iSP, contralateral & ipsilateral silent period; MEP, motor evoked potential; SICI, short interval intracortical inhibition; CRI, cortical reciprocal inhibition; MP, motor performance; FDI, first dorsal interosseous; APB, abductor pollicis brevis; AH, abductor hallucis; EDC, extensor digitorum communis; BIC, biceps brachii; ECR, extensor carpi radialis; FCR, flexor carpi radialis; y, young; o, old; MVC, maximal voluntary contraction; (a), active; (r), rest.

The TMS evoked silent period is an interruption of ongoing EMG activity after stimulating the contralateral M1 with TMS, and is believed to reflect the GABA-B mediated cortical inhibition [72]. Although the age-related changes in contralateral silent period reveal some inconsistencies, a general trend is a decrease in inhibition in old compared to young adults with four out of seven studies reporting a shorter and only one study a longer silent period. The inconsistencies can be related to between-study methodological differences, like the muscle investigated and selection of TMS parameters. There is also variation with respect to inhibition measured by the silent period according to task complexity. Execution of a simple wrist movement did not affect silent period duration in young and old adults but the silent period lengthened in young and shortened in old adults when they performed difficult coordination tasks [5]. Interestingly, within the old group low performers had a shorter silent period than high performers. Thus it might be speculated that the decrease in the silent period with ongoing age might be a compensatory strategy. However, it should be noted that the duration of the silent period correlates with the MEP size [73]. To rule out that differences in silent period are caused by differences in MEP size, a ratio between the two should be used. Oliviero et al. [68] found that the shortening of the silent period with aging disappears when the silent period duration is divided by MEP size. However, Sale and Semmler [69] and Fujiyama et al. [5] did not find such a relationship. Thus, it is difficult to draw any conclusions about the interrelation of changes in behavioral parameters and changes of the duration of the silent period with age at this stage.

SICI is, unlike the silent period, mediated by GABA-A receptors and measured with paired pulse TMS. Studies found inconsistent results regarding the effect of age on SICI. Two studies report increased SICI with aging [74,75], while two other studies report decreased SICI [6,71], and the rest report no effect [68,76-79]. Also here, inconsistencies are probably caused by methodological differences such as the selection of TMS parameters and the muscles examined. Across studies there is a wide variety of methods to set the conditioning and test pulse stimulation intensities, complicating comparisons between studies. Moreover, there seems to be an interaction between the size of the upper extremity muscle and age on the amount of inhibition, with less SICI in old adults [6,71] or no age-related changes [68,76] when examining intrinsic hand muscles and greater SICI in old adults when examining the larger wrist flexors and extensors [74,75]. Only one study [6] examined the correlation between the amount of SICI and behavioral measures. They reported that a weaker resting state SICI and less modulation in SICI during the movement preparation phase correlated with slower reaction times and alternating finger tapping.

Another type of inhibition is the inhibition of the corticospinal output to the antagonist muscle by afferent input from the agonist muscle (cortical reciprocal inhibition). This inhibition can be investigated by measuring the effect of peripheral afferent stimulation of the agonist muscle on TMS evoked MEP recorded in the antagonist muscle. At rest, the MEP in the extensor carpi radialis longus is inhibited by peripheral stimulation by about 40% in young adults, while no

inhibition is apparent in old adults [70]. This is interpreted as a decrease in cortical reciprocal inhibition with age, although influence of age-related changes in afferent input cannot be excluded. There are no studies linking cortical reciprocal inhibition with performance in motor tasks and it is also unclear if this form of inhibition is actually active during muscle contraction. It can be speculated, however, that the reduced cortical reciprocal inhibition has a role in the increased muscular coactivation seen in elderly subjects [80-82].

The emerging picture is that aging causes a reorganization of cortical control of voluntary movement, with an increase in brain activation and decrease in cortical inhibition. However, most of the studies focused on healthy elderly aged between 60 and 80 years, and do not allow to clearly consider functional changes in the oldest old (>80 years) and the effect of co-morbidities on the proposed reorganization of cortical motor control. Moreover, it is not known whether the changes in inhibitory circuits are related to the increased brain activation. Similarly, it is not clear whether these changes in inhibitory circuits result from malfunction, or serve a compensatory purpose. To fully understand age-related changes in motor control, future studies should focus on the relationship between brain activation, the different forms of inhibition, and motor performance and determine if exercise modifies motor function and elements of the inhibitory system in a correlated manner. Combining TMS and brain imaging techniques would provide valuable data for the purpose of answering these questions.

5. RELATIONSHIP BETWEEN STRUCTURAL AND FUNCTIONAL CHANGES AND POSTURAL CONTROL IN AGING

In the first section we argued that posture is not only controlled by spinal reflexes, but is also influenced by cortical structures. Hence, it seems inevitable that the age-related changes in the spinal and cortical systems, as reviewed in the previous sections, have an impact on postural control in old adults. Therefore, we will discuss the possibility that the structural and functional changes in the aging neuromotor system are linked to the deterioration of postural control in old adults (Figure 1), leading to the conclusion that aging causes a reorganization of postural control.

5.1. Cortical structural changes and postural control

Many studies report that changes in cortical structures (brain atrophy, cortical thinning, and/or white matter hyperintensity) negatively correlate with performance in postural tasks. In these studies postural control was quantified based on single leg stance time [83,84], postural sway [84-86], history of falls [87,88], Tinetti gait and balance score [88,89], slowing of gait [90,91], and the short physical performance battery (SPPB) [83,87,92].

Gray and white matter degeneration can interfere with postural control through the slowing in information processing speed. Rosano et al. [93] demonstrated that the association between reduced prefrontal area volume and slowing of gait is explained by slower information

processing, quantified by the Digit Symbol Substitution Test (DSST). Moreover, neuropsychological function mediates the relationship between white matter hyperintensities and choice stepping performance under dual task conditions [94]. In this study neuropsychological function was measured with the DSST, the trail making test, and the grooved pegboard test, together indicating information processing speed and attention capacity.

5.2. Response time and postural control

Old adults respond to platform perturbations with longer muscle onset latencies that delay postural corrections [95-97]. Tilting or translating a horizontal platform on which people stand, elicit short (SLR) and long (LLR) latency responses. The age-related increase of 5 ms in SLR latencies is similar to the 3-7 ms difference in H-reflex latency [36,97,98]. The prolongation in SLR latency can therefore be explained by reduced conduction velocity mediated by a loss in myelination [33]. Age-related delays in LLR are even more pronounced (20 ms), and thus cannot be explained by peripheral changes alone [97,99]. Consequently, there must be an increase in central processing time. Both the soleus SLR and LLR latencies are correlated with sway area after stance perturbation [97], pointing to the behavioral significance of these response latencies and feedback control. Delayed postural corrections in old adults can thus be explained by functional deterioration in conduction and processing speed due to structural changes.

5.3. Age-related reorganization of postural control

Whereas many studies have shown a greater activation of M1, prefrontal, and premotor areas and decreased cortical inhibition during upper extremity tasks, little is known about whether similar reorganizations occur during postural control. Zwergal et al. [31] examined brain activation patterns with fMRI while young and old adults imagined that they were standing, walking and running. The age-related differences in brain activation were most prominent in standing, followed by walking and running. During imagined standing, a relative increase in activation with age was evident in numerous multisensory areas; the bilateral posterior insulae, superior and middle temporal gyri, inferior frontal gyri, fusiform and lingual gyri, MT/V5 areas, and the postcentral gyri. In young adults, activation of one sensory modality suppressed activation of other sensory modalities [100,101]. This phenomenon, called inhibitory reciprocal interaction of sensory systems, is thought to decrease with age [102,103]. A decrease in inhibitory reciprocal interaction could be used to explain the enhanced cortical sensory representation observed by Zwergal et al. [31]. It is suggested that this is a compensatory strategy for a decline in the unimodal sensory systems. In line with this hypothesis, Goble et al. [104] observed 71% lower activation after muscle spindle stimulation in the right putamen of old compared to young adults, and the activity of this structure was positively related to performance on a proprioceptive joint position sense test in both age groups. The relationship between putamen activation and position sense was mediated

by decreased white matter integrity in old adults.

In summary, similarly to manual tasks, old adults appear to use the increased activation strategy in postural tasks in compensation for structural and/or functional changes in other areas. Therefore, one element of the age-related reorganization of postural control is the increased brain activation. A clear distinction between the non-postural and postural data is that in postural tasks the age-related increase in activation occurred in sensory rather than motor areas involved in postural control, possibly due to the fact that the postural task was imaginary. A second element of the age-related reorganization of postural control is the decrease in inhibitory reciprocal interaction of sensory systems. However, whether motor cortical inhibition in its various forms (SICI, silent period, interhemispheric inhibition) also becomes weaker with aging during a postural task is not known and is a promising topic for future research.

One of the behavioral consequences of increased activation and decreased inhibition could be the use of a heightened coactivation strategy. Old adults execute many voluntary movements with increased antagonistic activity, including hand or arm movements [105-107], quiet standing [108,109], and when perturbed while standing [110]. The mechanisms underlying this coactivation are probably both spinal and cortical [111]. For example, potential mechanisms involve the reduction of spinal [112] and cortical [70] reciprocal inhibition with age, although these studies did not examine whether the increased antagonist activation was associated with either form of inhibition. Another potential cortical mechanism underlying the increased coactivation is the observed increased activation of motor and premotor brain areas in old adults. These areas include the antagonist representation area, resulting in greater activation of cortical neurons controlling the antagonistic muscle activity. As discussed before, this increased activation is probably the result of a shift in the balance between the activation of cortical inhibitory and excitatory circuits toward excitation in old adults. Although it seems plausible to link increased activation and decreased inhibition to coactivation, this relationship has not been confirmed.

Another behavioral consequence of the described functional changes could be the consistently higher interference of a cognitive task on postural control in old adults [113-116]. The cortical involvement during dual tasks in young adults has been investigated using fMRI and TMS techniques. For example, Wu et al. [117] examined dual task-associated neural activity when subjects performed a finger tapping and a counting task. They observed that two cerebellar regions and the precuneus were only activated in dual task conditions but not during single task performance. This demonstrates that additional brain areas are recruited to integrate the two tasks. Others found no dual-task specific brain areas, but an increased activation of the areas that are active in both single tasks [118]. TMS studies show that performing a motor task in upper (or lower) extremity increases corticospinal excitability [119] and decreases corticospinal inhibition [120] to lower (or upper) extremity muscles. Although this activity-dependent coupling may mediate some of the dual task interference in dual motor tasks, it is not sensitive to several task mod-

ulations that do influence behavioral outcome measures [119]. Therefore, it must be concluded that other factors are more important in dual-task interference. On the spinal level, a recent study suggests that increasing the difficulty of a cognitive task does not influence the H-reflex amplitude during a postural dual task in young and elderly adults [121]. Accordingly, the age-related differences in dual-task performance did not involve a change in the efficacy of homonymous Ia afferents to discharge motor neurons in young and elderly adults.

A common theory explaining dual task interference is the central capacity-sharing model. This model predicts that the resources are limited to execute both tasks concurrently [122]. Old adults might have a reduced residual capacity because of decreased availability of resources and increased neural recruitment (see sections 3.2 & 4.2). Van Impe et al. [118] tested the hypothesis that the reduced residual capacity causes the age-related increase in dual task interference and found that both young and old adults were able to upregulate their brain activity in the common areas for dual- as compared to single-task performance. This means that, at least in these tasks, central capacity limited young and old adults to a similar extent. However, the cognitive task (arithmetic addition) might not have been challenging enough to reach the central capacity limit since there were no age-related differences in dual task costs, nor in brain activity associated with the cognitive task.

Van Impe et al. [86] examined the neural correlates of dual task performance involving a postural task in young and old adults. The increase in the error rate while performing a mental rotation task in standing as compared to sitting was higher in old compared with young adults. Interestingly, in old adults activation in the left lingual gyrus during the mental rotation task while lying in the scanner correlated with the change in performance from the seated to the standing position outside of the scanner ($r = -0.83$, $p < 0.05$), so that more activation was associated with better performance. This finding is in contradiction with the hypothesis that increased neural recruitment leads to reduced residual capacity and results in greater dual task interference, but is in line with the theory that the increased activation seen in old adults acts as a compensatory mechanism.

In summary, the age-related reorganization in cortical motor control during voluntary tasks, characterized by greater brain activation and reduced inhibition, is also present during postural tasks. Further research will determine whether in addition to sensory areas, age also affects the function of motor areas during postural tasks. Further, there is the need to better understand whether the age-related increase in antagonist muscle coactivation during postural tasks exacts functional costs. Although theories have been proposed that greater activation mediates the age-related increase in dual task interference, so far scientific evidence is lacking.

5.4. Spinal versus supraspinal postural control mechanisms

As discussed in section 4.1, old compared to young adults appear to have a different relative con-

tribution of supraspinal and spinal inputs to the gain control of motor output during a voluntary task. Also during postural tasks, the control of spinal reflexes differs between young and old adults. In young adults, greater postural instability is associated with greater down regulation of the H-reflex [123], presumably through presynaptic inhibition [124]. It is thought that the down-regulation in the H-reflex prevents postural disturbance [125]. In old adults, H-reflexes are lower and the modulation of the H-reflex with increasing postural task difficulty is either the opposite of what is observed in young adults (upregulation) [126] or the reflex modulation is absent [123]. According to Koceja et al. [123] the reflex upregulation or the absence of it is accompanied by a decreased ability of old adults to modulate presynaptic inhibition. In contrast, Baudry and Duchateau [108] observed greater upregulation of presynaptic inhibition in old adults compared to young adults with increasing task difficulty, suggesting a feedforward mechanism that reduces spinal contribution and thus increases supraspinal contribution in difficult postural tasks. Furthermore, the amount of presynaptic inhibition was associated with sway amplitude in the sagittal plane and coactivation of leg muscles in old adults, so that greater Ia presynaptic inhibition was accompanied by greater sway amplitude and greater coactivation, suggesting an age-related depression of the inputs from muscle afferents compensated by an augmentation of coactivation among leg muscles during the control of upright stance [108]. This could be related to the greater level of muscle activation that limits muscle lengthening and shortening and therefore the relevance of spindle afferents [127]. Furthermore, a recent study reports lower efficacy of Ia afferents to discharge spinal motor neurons accompanied by greater corticospinal excitability in elderly adults, indicating an increased contribution of the descending drive in controlling soleus activity during upright standing with aging [128]. In conclusion, studies suggest that an additional element of age-related reorganization of postural control is an alteration in the control of presynaptic inhibition in postural tasks, although the direction of this alteration is inconsistent and/or the modulating extrinsic (e.g., postural task, task difficulty) and intrinsic factors (e.g., back pain, impaired vision) are not yet known. Furthermore, to date, only cross-sectional studies are available so that there are no data showing changes of neural control mechanisms with age.

Another approach to examine the role of spinal reflexes in the control of standing posture is to move the support surface on which subjects stand. Most studies showed that the amplitude of the early response was smaller and the late response was higher in old compared with young adults [95,99]. The observation of smaller early responses is consistent with the age-related decrease in H-reflex amplitude in the soleus [108,126]. However, smaller H-reflexes were not observed in the tibialis muscle at rest or during small voluntary contractions [129]. Therefore, the reduced postural response in the tibialis anterior may indicate a specific downmodulation in upright standing. Furthermore, as the early responses (short- and medium latency responses) are mediated via spinal reflex circuits but long-latency responses also involve supraspinal structures [27], the shift toward later responses with aging may suggest a change in the contribution of spi-

nal and supraspinal mechanisms when standing posture is experimentally perturbed.

Together with the findings of increased cortical activation during postural tasks and the increased dual task interference with aging, there is some evidence suggesting that old compared with young adults rely less on spinal reflexes and more on cortical activation than young adults for postural control, although this remains to be fully explored. The reason for a reduced reliance on spinal reflexes is not known. Among the candidates is the prominent reduction in conduction velocity and degeneration of somatosensory receptors [130,131] that contribute to a decreased relevance of afferent inputs and therefore reduces the reflex efficiency of spinal reflex in postural control. Although these impairments also affect supraspinal responses, we speculate that the high degrees of freedom in the supraspinal mechanism afford old adults flexibility to compensate for neuromuscular impairments. Another possible explanation for a reduced reliance on spinal reflexes is the difference in relative task difficulty; the same postural task is more difficult for old than for young adults. Indeed, when young individuals encounter increasingly difficult postural tasks, spinal reflexes become attenuated [123].

6. PLASTICITY OF POSTURAL CONTROL MECHANISMS

Balance training improves old adults' postural control [132,133]. However, neural correlates of balance training, demonstrating plasticity of postural control mechanisms, have mostly been studied in young subjects. Several electrophysiological studies have found task specific decreased cortical excitability induced by balance training, indicating cortical plasticity [134-136]. In one study, the training induced changes in cortical measures were correlated with the changes in postural performance so that subjects who had a greater reduction in cortical excitability, improved their postural performance more [136]. This study also showed a phase-specific adaptation of the soleus H-reflex. Balance training decreased the amplitude of the H-reflex elicited at the time of the LLR but not at the SLR. The authors favored the explanation that supraspinally induced presynaptic inhibition was selectively increased at the time of the LLR that was previously shown to be transcortically mediated [27]. Thus, adaptation of supraspinal processing in response to balance training seems to be responsible for both alterations of spinal reflex circuits and descending motor commands.

Imaging studies support the idea that cortical and subcortical adaptations play a putative role in improving postural control after balance training. In a cross-sectional study, the hippocampus structure was different between female dancers and slackliners and recreationally active females [137]. This may indicate that long-term training involving demanding postural tasks leads to structural changes of the brain. Recent imaging data obtained during balance training support this view and highlight that structural changes in gray and white matter volume in response to balance exercises may occur very rapidly [138]. The authors recorded brain images after every second training session and displayed rapid transient gray matter changes in sensorimotor areas

(after 2 training sessions) and more slowly evolving increases in parts of the orbitofrontal cortex (after 6 training sessions). Interestingly, there was a positive linear correlation between gray matter expansion in the left supplementary motor area (SMA) and the ability to balance on the training device, an unstable moving platform. In a subsequent study involving the same subjects and the same structural data, the authors demonstrated an association between these structural gray matter alterations and changes in functional connectivity of prefrontal and supplementary-motor areas [139]. Therefore, there is strong evidence that the morphological adaptations are functionally relevant with respect to alterations in postural control. Furthermore, these studies emphasize that structural adaptations occur very rapidly in response to balance training. Finally, one single balance training session of 45 min, incorporating 15, 30-s-long balancing trials resulting in 7.5 min effective training time, is sufficient to induce macroscopic structural changes in areas belonging to the vestibular cortical system (Taubert et al. 2013 OHMB). Thus, both electrophysiological and imaging studies illustrate that cortical adaptations occur in response to balance training and that these changes are of high functional relevance.

To the best of our knowledge, there are no studies that examined age-related differences in cortical adaptations to balance interventions. There are, however, two recent papers that provide preliminary insights into the neural plasticity associated with balance training in old adults [140,141]. In these papers, the healthy old adults served as controls for Parkinson and cerebellar patients. Sehm et al. (2014) report a positive linear correlation between changes in left hippocampus volume and balance performance after training of a dynamic balancing task. Burciu et al. (2013) report a trend for gray matter volume increases in several cortical (occipital cortex and superior temporal gyrus) and subcortical (left putamen and hippocampus, right cerebellum, VIIIb) structures, after 2 weeks of balance training consisting of weight shifting exercises. Although a direct comparison with young adults is missing, these results do suggest that structural plasticity is still present in the aging brain.

Considering spinal adaptations, the limited data suggest that the nature of adaptation to exercise training is similar in young and old adults. For instance, Mynark and Koceja [142] tested subjects' ability to down train the soleus H-reflex because high H-reflex amplitude tends to destabilize upright stance. Old compared with young adults were able to reduce the H-reflex to a similar extent. At the same time, postural stability improved in both groups. In another study with elderly participants, Granacher et al. [143] demonstrated changes in postural (spinal) reflex responses that were accompanied by an improved ability to compensate for postural disturbances. Thus, the central nervous system of elderly people shows plasticity in response to postural exercises. It is not yet known whether such adaptations differ in magnitude or follow a different time course compared to in young adults.

7. CONCLUSIONS

In young adults it is established that the cerebral cortex contributes to postural control of undisturbed and disturbed standing. Therefore, the degeneration and accompanying functional changes in the brain seen in motor control of simple manual tasks are also operational under postural tasks and likely to influence postural control. Indeed, gray and white matter loss with aging is associated with decreased performance in postural tasks. Moreover, there is a reorganization of cortical and spinal control of posture with aging including increased cortical activation, cortical disinhibition, and differential control of spinal reflexes. The structure-function-behavior model in Figure 1 highlights the need for future studies to incorporate behavioral measures to document how these age-related structural and functional changes influence postural control. In general, we recommend future studies to include at least two of the three domains in the model, to be able to examine associations between domains. This method can for example be applied to test the hypotheses that the age-related spinal and cortical functional changes underlie the greater amount of co-activation and decreased dual task performance seen in old adults during postural tasks. Eventually, the plasticity of the aging neuromotor system controlling posture should be examined using balance training.

REFERENCES

1. Bernard JA, Seidler RD. Evidence for motor cortex dedifferentiation in older adults. Neurobiol Aging 2012 Sep;33(9):1890-1899.

2. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008 Jan 2;28(1):91-99.

3. Fling BW, Seidler RD. Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. Cereb Cortex 2012 Nov;22(11):2643-2652.

4. Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. Brain 2003 Apr;126(Pt 4):873-888.

5. Fujiyama H, Hinder MR, Schmidt MW, Garry MI, Summers JJ. Age-related differences in corticospinal excitability and inhibition during coordination of upper and lower limbs. Neurobiol Aging 2012 Jul;33(7):1484.e1-1484.14.

6. Heise KF, Zimerman M, Hoppe J, Gerloff C, Wegscheider K, Hummel FC. The Aging Motor System as a Model for Plastic Changes of GABA-Mediated Intracortical Inhibition and Their Behavioral Relevance. J Neurosci 2013 May 22;33(21):9039-9049.

7. Visser JE, Bloem BR. Role of the basal ganglia in balance control. Neural Plast 2005;12(2-3):161-74; discussion 263-72.

8. Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. Brain 1999 Feb;122 (Pt 2)(Pt 2):329-338.

9. Horak FB, Diener HC. Cerebellar control of postural scaling and central set in stance. J Neurophysiol 1994 Aug;72(2):479-493.

10. Cham R, Perera S, Studenski SA, Bohnen NI. Striatal dopamine denervation and sensory integration for balance in middle-aged and older adults. Gait Posture 2007 Oct;26(4):516-525.

11. Murray ME, Senjem ML, Petersen RC, Hollman JH, Preboske GM, Weigand SD, et al. Functional impact of white matter hyperintensities in cognitively normal elderly subjects. Arch Neurol 2010 Nov;67(11):1379-1385.

12. Rosano C, Aizenstein HJ, Studenski S, Newman AB. A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2007 Sep;62(9):1048-1055.

13. Woollacott MH, Bonnet M, Yabe K. Preparatory process for anticipatory postural adjustments: modulation of leg muscles reflex pathways during preparation for arm movements in standing man. Exp Brain Res 1984;55(2):263-271.

14. Horak FB, Diener HC, Nashner LM. Influence of central set on human postural responses. J Neurophysiol 1989 Oct;62(4):841-853.

15. Morasso PG, Schieppati M. Can muscle stiffness alone stabilize upright standing? J Neurophysiol 1999 Sep;82(3):1622-1626.

16. Loram ID, Maganaris CN, Lakie M. Human postural sway results from frequent, ballistic bias impulses by soleus and gastrocnemius. J Physiol 2005 Apr 1;564(Pt 1):295-311.

17. Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 1910 Apr 26;40(1-2):28-121.

18. Jacobs JV, Horak FB. Cortical control of postural responses. J Neural Transm 2007;114(10):1339-1348.

19. Taube W, Gruber M, Gollhofer A. Spinal and supraspinal adaptations associated with balance training and their functional relevance. Acta Physiol (Oxf) 2008 Jun;193(2):101-116.

20. Bard P. Studies on the cerebral cortex I. Localized control of placing and hopping reactions in the cat and their normal management by small cortical remnants. Arch Neurol Psychiatry 1933;30(1):40-74.

21. Brooks CM. Studies on the cerebral cortex II. Localized representation of hopping and placing reactions in the rat. Am J Physiol Legacy Content 1933;105(1):162-171.

22. Geurts AC, de Haart M, van Nes IJ, Duysens J. A review of standing balance recovery from stroke. Gait Posture 2005;22(3):267-281.

23. Diener HC, Ackermann H, Dichgans J, Guschlbauer B. Medium- and long-latency responses to displacements of the ankle joint in patients with spinal and central lesions. Electroencephalogr Clin Neurophysiol 1985 May;60(5):407-416.

24. Hyndman D, Ashburn A. People with stroke living in the community: Attention deficits, balance, ADL ability and falls. Disabil Rehabil 2003 Aug 5;25(15):817-822.

25. Jacobs JV, Fujiwara K, Tomita H, Furune N, Kunita K, Horak FB. Changes in the activity of the cerebral cortex relate to postural response modification when warned of a perturbation. Clin Neurophysiol 2008 Jun;119(6):1431-1442.

26. Slobounov S, Hallett M, Stanhope S, Shibasaki H. Role of cerebral cortex in human postural control: an EEG study. Clin Neurophysiol 2005 Feb;116(2):315-323.

27. Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A. Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. J Appl Physiol 2006 Aug;101(2):420-429.

28. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of human standing. Acta Physiol (Oxf) 2009 Mar;195(3):385-395.

29. Soto O, Valls-Sole J, Shanahan P, Rothwell J. Reduction of intracortical inhibition in soleus muscle during postural activity. J Neurophysiol 2006 Oct;96(4):1711-1717.

30. Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: A PET study. Hum Brain Mapp 2003;19(1):47-62.

31. Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiol Aging 2012 Jun;33(6):1073-1084.

32. Goble DJ, Coxon JP, Van Impe A, Geurts M, Doumas M, Wenderoth N, et al. Brain activity during ankle proprioceptive stimulation predicts balance performance in young and older adults. J Neurosci 2011 Nov 9;31(45):16344-16352.

33. Verdu E, Ceballos D, Vilches JJ, Navarro X. Influence of aging on peripheral nerve function and regeneration. J Peripher Nerv Syst 2000 Dec;5(4):191-208.

34. Ceballos D, Cuadras J, Verdu E, Navarro X. Morphometric and ultrastructural changes with ageing in mouse peripheral nerve. J Anat 1999 Nov;195 (Pt 4)(Pt 4):563-576.

35. Jacobs JM, Love S. Qualitative and quantitative morphology of human sural nerve at different ages. Brain 1985 Dec;108 (Pt 4)(Pt 4):897-924.

36. Scaglioni G, Narici MV, Maffiuletti NA, Pensini M, Martin A. Effect of ageing on the electrical and mechanical properties of human soleus motor units activated by the H reflex and M wave. J Physiol 2003 Apr 15;548(Pt 2):649-661.

37. Kararizou E, Manta P, Kalfakis N, Vassilopoulos D. Morphometric study of the human muscle spindle. Anal Quant Cytol Histol 2005 Feb;27(1):1-4.

38. McNeil CJ, Doherty TJ, Stashuk DW, Rice CL. Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. Muscle Nerve 2005 Apr;31(4):461-467.

39. Brooks SV, Faulkner JA. Skeletal muscle weakness in old age: underlying mechanisms. Med Sci Sports Exerc 1994 Apr;26(4):432-439.

40. Stalberg E, Fawcett PR. Macro EMG in healthy subjects of different ages. J Neurol Neurosurg Psychiatry 1982 Oct;45(10):870-878.

41. Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch Gen Psychiatry 2001 May;58(5):461-465.

42. Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am J Neuroradiol 2002 Sep;23(8):1327-1333.

43. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, et al. Thinning of the cerebral cortex in aging. Cereb Cortex 2004 Jul;14(7):721-730.

44. Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol Aging 2004 Mar;25(3):377-396.

45. McGinnis SM, Brickhouse M, Pascual B, Dickerson BC. Age-related changes in the thickness of cortical zones in humans. Brain Topogr 2011 Oct;24(3-4):279-291.

46. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 2003 Apr 15;23(8):3295-3301.

47. Morrison JH, Hof PR. Life and death of neurons in the aging brain. Science 1997 Oct 17;278(5337):412-419.

48. Kennedy KM, Raz N. Age, sex and regional brain volumes predict perceptual-motor skill acquisition. Cortex 2005 Aug;41(4):560-569.

49. Sridharan A, Willette AA, Bendlin BB, Alexander AL, Coe CL, Voytko ML, et al. Brain volumetric and microstructural correlates of executive and motor performance in aged rhesus monkeys. Front Aging Neurosci 2012;4:31.

50. Sullivan EV, Pfefferbaum A. Diffusion tensor imaging and aging. Neurosci Biobehav Rev 2006;30(6):749-761.

51. Ota M, Obata T, Akine Y, Ito H, Ikehira H, Asada T, et al. Age-related degeneration of corpus callosum measured with diffusion tensor imaging. Neuroimage 2006 Jul 15;31(4):1445-1452.

52. Jarbo K, Verstynen T, Schneider W. In vivo quantification of global connectivity in the human corpus callosum. Neuroimage 2012 Feb 1;59(3):1988-1996.

53. Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, et al. Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci 2007 Nov 7;27(45):12132-12138.

54. Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, et al. Equivalent disruption of regional white matter microstructure in ageing healthy men and women. Neuroreport 2001 Jan 22;12(1):99-104.

55. Kerchner GA, Racine CA, Hale S, Wilheim R, Laluz V, Miller BL, et al. Cognitive processing speed in older adults: relationship with white matter integrity. PLoS One 2012;7(11):e50425.

56. Rivner MH, Swift TR, Malik K. Influence of age and height on nerve conduction. Muscle Nerve 2001;24(9):1134-1141.

57. Skinner HB, Barrack RL, Cook SD. Age-related decline in proprioception. Clin Orthop Relat Res 1984 Apr;184(184):208-211.

58. Earles D, Vardaxis V, Koceja D. Regulation of motor output between young and elderly subjects. Clin Neurophysiol 2001 Jul;112(7):1273-1279.

59. Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002 Feb 26;58(4):630-635.

60. Langan J, Peltier SJ, Bo J, Fling BW, Welsh RC, Seidler RD. Functional implications of age differences in motor system connectivity. Front Syst Neurosci 2010 Jun 7;4:17.

61. McGregor KM, Zlatar Z, Kleim E, Sudhyadhom A, Bauer A, Phan S, et al. Physical activity and neural correlates of aging: a combined TMS/fMRI study. Behav Brain Res 2011 Sep 12;222(1):158-168.

62. Sohn YH, Jung HY, Kaelin-Lang A, Hallett M. Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. Exp Brain Res 2003 Jan;148(2):176-185.

63. Calautti C, Serrati C, Baron JC. Effects of age on brain activation during auditory-cued thumb-to-index

opposition: A positron emission tomography study. Stroke 2001 Jan;32(1):139-146.

64. Wu T, Hallett M. The influence of normal human ageing on automatic movements. J Physiol 2005 Jan 15;562(Pt 2):605-615.

65. Ward NS, Swayne OB, Newton JM. Age-dependent changes in the neural correlates of force modulation: an fMRI study. Neurobiol Aging 2008 Sep;29(9):1434-1446.

66. Talelli P, Ewas A, Waddingham W, Rothwell JC, Ward NS. Neural correlates of age-related changes in cortical neurophysiology. Neuroimage 2008 May 1;40(4):1772-1781.

67. Arthurs OJ, Boniface S. How well do we understand the neural origins of the fMRI BOLD signal? Trends Neurosci 2002 Jan;25(1):27-31.

68. Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, et al. Effects of aging on motor cortex excitability. Neurosci Res 2006 May;55(1):74-77.

69. Sale MV, Semmler JG. Age-related differences in corticospinal control during functional isometric contractions in left and right hands. J Appl Physiol 2005 Oct;99(4):1483-1493.

70. Hortobagyi T, del Olmo MF, Rothwell JC. Age reduces cortical reciprocal inhibition in humans. Exp Brain Res 2006 May;171(3):322-329.

71. Marneweck M, Loftus A, Hammond G. Short-interval intracortical inhibition and manual dexterity in healthy aging. Neurosci Res 2011 Aug;70(4):408-414.

72. Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 1999 Jun 1;517(Pt 2):591-597.

73. Orth M, Rothwell JC. The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. Clin Neurophysiol 2004 May;115(5):1076-1082.

74. McGinley M, Hoffman RL, Russ DW, Thomas JS, Clark BC. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. Exp Gerontol 2010 Sep;45(9):671-678.

75. Kossev AR, Schrader C, Dauper J, Dengler R, Rollnik JD. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. Neurosci Lett 2002 Nov 22;333(2):83-86.

76. Smith AE, Ridding MC, Higgins RD, Wittert GA, Pitcher JB. Cutaneous afferent input does not modulate motor intracortical inhibition in ageing men. Eur J Neurosci 2011 Nov;34(9):1461-1469.

77. Rogasch NC, Dartnall TJ, Cirillo J, Nordstrom MA, Semmler JG. Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. J Appl Physiol 2009 Dec;107(6):1874-1883.

78. Cirillo J, Rogasch NC, Semmler JG. Hemispheric differences in use-dependent corticomotor plasticity in young and old adults. Exp Brain Res 2010 Aug;205(1):57-68.

79. Stevens-Lapsley JE, Thomas AC, Hedgecock JB, Kluger BM. Corticospinal and intracortical excitability of the quadriceps in active older and younger healthy adults. Arch Gerontol Geriatr 2013 Jan-Feb;56(1):279-284.

80. Darling WG, Cooke JD, Brown SH. Control of simple arm movements in elderly humans. Neurobiol Aging 1989 Mar-Apr;10(2):149-157.

81. Benjuya N, Melzer I, Kaplanski J. Aging-induced shifts from a reliance on sensory input to muscle cocontraction during balanced standing. J Gerontol A Biol Sci Med Sci 2004 Feb;59(2):166-171.

82. Baudry S, Maerz AH, Enoka RM. Presynaptic modulation of Ia afferents in young and old adults when performing force and position control. J Neurophysiol 2010 Feb;103(2):623-631.

83. Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology 2008 Mar 18;70(12):935-942.

84. Kido T, Tabara Y, Igase M, Ochi N, Uetani E, Nagai T, et al. Postural instability is associated with brain atrophy and cognitive impairment in the elderly: the J-SHIPP study. Dement Geriatr Cogn Disord 2010;29(5):379-387.

85. Sullivan EV, Rose J, Rohlfing T, Pfefferbaum A. Postural sway reduction in aging men and women: relation to brain structure, cognitive status, and stabilizing factors. Neurobiol Aging 2009 May;30(5):793-807.

86. Van Impe A, Coxon JP, Goble DJ, Doumas M, Swinnen SP. White matter fractional anisotropy predicts balance performance in older adults. Neurobiol Aging 2012 Sep;33(9):1900-1912.

87. Ryberg C, Rostrup E, Paulson OB, Barkhof F, Scheltens P, van Straaten EC, et al. Corpus callosum atrophy as a predictor of age-related cognitive and motor impairment: a 3-year follow-up of the LADIS study cohort. J Neurol Sci 2011 Aug 15;307(1-2):100-105.

88. Kerber KA, Enrietto JA, Jacobson KM, Baloh RW. Disequilibrium in older people: a prospective study. Neurology 1998 Aug;51(2):574-580.

89. Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. Arch Neurol 2003 Jun;60(6):835-839.

90. de Laat KF, Reid AT, Grim DC, Evans AC, Kotter R, van Norden AG, et al. Cortical thickness is associated with gait disturbances in cerebral small vessel disease. Neuroimage 2012 Jan 16;59(2):1478-1484.

91. Rosano C, Sigurdsson S, Siggeirsdottir K, Phillips CL, Garcia M, Jonsson PV, et al. Magnetization transfer imaging, white matter hyperintensities, brain atrophy and slower gait in older men and women. Neurobiol Aging 2010 Jul;31(7):1197-1204.

92. Guttmann CR, Benson R, Warfield SK, Wei X, Anderson MC, Hall CB, et al. White matter abnormalities in mobility-impaired older persons. Neurology 2000 Mar 28;54(6):1277-1283.

93. Rosano C, Studenski SA, Aizenstein HJ, Boudreau RM, Longstreth WT,Jr, Newman AB. Slower gait, slower information processing and smaller prefrontal area in older adults. Age Ageing 2012 Jan;41(1):58-64.

94. Zheng JJ, Delbaere K, Close JC, Sachdev PS, Wen W, Lord SR. White matter hyperintensities and impaired choice stepping reaction time in older people. Neurobiol Aging 2012 Jul;33(7):1177-1185.

95. Lin SI, Woollacott MH. Postural muscle responses following changing balance threats in young, stable older, and unstable older adults. J Mot Behav 2002 Mar;34(1):37-44.

96. Tokuno CD, Cresswell AG, Thorstensson A, Carpenter MG. Age-related changes in postural responses revealed by support-surface translations with a long acceleration-deceleration interval. Clin Neurophysiol 2010 Jan;121(1):109-117.

97. Nardone A, Siliotto R, Grasso M, Schieppati M. Influence of aging on leg muscle reflex responses to stance perturbation. Arch Phys Med Rehabil 1995 Feb;76(2):158-165.

98. Sabbahi MA, Sedgwick EM. Age-related changes in monosynaptic reflex excitability. J Gerontol 1982 Jan;37(1):24-32.

99. Allum JH, Carpenter MG, Honegger F, Adkin AL, Bloem BR. Age-dependent variations in the directional

sensitivity of balance corrections and compensatory arm movements in man. J Physiol 2002 Jul 15;542(Pt 2):643-663.

100. Brandt T, Bartenstein P, Janek A, Dieterich M. Reciprocal inhibitory visual-vestibular interaction. Visual motion stimulation deactivates the parieto-insular vestibular cortex. Brain 1998 Sep;121(Pt 9):1749-1758.

101. Laurienti PJ, Burdette JH, Wallace MT, Yen YF, Field AS, Stein BE. Deactivation of sensory-specific cortex by cross-modal stimuli. J Cogn Neurosci 2002 Apr 1;14(3):420-429.

102. Townsend J, Adamo M, Haist F. Changing channels: an fMRI study of aging and cross-modal attention shifts. Neuroimage 2006 Jul 15;31(4):1682-1692.

103. Peiffer AM, Hugenschmidt CE, Maldjian JA, Casanova R, Srikanth R, Hayasaka S, et al. Aging and the interaction of sensory cortical function and structure. Hum Brain Mapp 2009 Jan;30(1):228-240.

104. Goble DJ, Coxon JP, Van Impe A, Geurts M, Van Hecke W, Sunaert S, et al. The neural basis of central proprioceptive processing in older versus younger adults: an important sensory role for right putamen. Hum Brain Mapp 2012 Apr;33(4):895-908.

105. Burnett RA, Laidlaw DH, Enoka RM. Coactivation of the antagonist muscle does not covary with steadiness in old adults. J Appl Physiol 2000 Jul;89(1):61-71.

106. Klein CS, Rice CL, Marsh GD. Normalized force, activation, and coactivation in the arm muscles of young and old men. J Appl Physiol 2001 Sep;91(3):1341-1349.

107. Seidler-Dobrin RD, He J, Stelmach GE. Coactivation to reduce variability in the elderly. Motor Control 1998 Oct;2(4):314-330.

108. Baudry S, Duchateau J. Age-related influence of vision and proprioception on Ia presynaptic inhibition in soleus muscle during upright stance. J Physiol 2012 Nov 1;590(Pt 21):5541-5554.

109. Nagai K, Yamada M, Uemura K, Yamada Y, Ichihashi N, Tsuboyama T. Differences in muscle coactivation during postural control between healthy older and young adults. Arch Gerontol Geriatr 2011 Nov-Dec;53(3):338-343.

110. Manchester D, Woollacott M, Zederbauer-Hylton N, Marin O. Visual, vestibular and somatosensory contributions to balance control in the older adult. J Gerontol 1989 Jul;44(4):M118-27.

111. Hortobagyi T, Devita P. Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. Exerc Sport Sci Rev 2006 Jan;34(1):29-35.

112. Kido A, Tanaka N, Stein RB. Spinal excitation and inhibition decrease as humans age. Can J Physiol Pharmacol 2004 Apr;82(4):238-248.

113. Rapp MA, Krampe RT, Baltes PB. Adaptive task prioritization in aging: selective resource allocation to postural control is preserved in Alzheimer disease. Am J Geriatr Psychiatry 2006 Jan;14(1):52-61.

114. Huxhold O, Li SC, Schmiedek F, Lindenberger U. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. Brain Res Bull 2006 Apr 14;69(3):294-305.

115. Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. J Gerontol A Biol Sci Med Sci 1997 Jul;52(4):M232-40.

116. Marsh AP, Geel SE. The effect of age on the attentional demands of postural control. Gait Posture 2000 Oct;12(2):105-113.

117. Wu T, Liu J, Hallett M, Zheng Z, Chan P. Cerebellum and integration of neural networks in dual-task processing. Neuroimage 2013 Jan 15;65:466-475.

118. Van Impe A, Coxon JP, Goble DJ, Wenderoth N, Swinnen SP. Age-related changes in brain activation underlying single- and dual-task performance: visuomanual drawing and mental arithmetic. Neuropsychologia 2011 Jul;49(9):2400-2409.

119. Hiraga CY, Garry MI, Carson RG, Summers JJ. Dual-task interference: attentional and neurophysiological influences. Behav Brain Res 2009 Dec 14;205(1):10-18.

120. Sohn YH, Kang SY, Hallett M. Corticospinal disinhibition during dual action. Exp Brain Res 2005 Mar;162(1):95-99.

121. Baudry S, Gaillard V. Cognitive demand does not influence the responsiveness of homonymous Ia afferents pathway during postural dual task in young and elderly adults. Eur J Appl Physiol 2013 Nov 19;114:295-303.

122. Tombu M, Jolicoeur P. A central capacity sharing model of dual-task performance. J Exp Psychol Hum Percept Perform 2003 Feb;29(1):3-18.

123. Koceja DM, Mynark RG. Comparison of heteronymous monosynaptic Ia facilitation in young and elderly subjects in supine and standing positions. Int J Neurosci 2000 Jul-Aug;103(1-4):1-17.

124. Katz R, Meunier S, Pierrot-Deseilligny E. Changes in presynaptic inhibition of Ia fibres in man while standing. Brain 1988 Apr;111(Pt 2):417-437.

125. Llewellyn M, Yang JF, Prochazka A. Human H-reflexes are smaller in difficult beam walking than in normal treadmill walking. Exp Brain Res 1990;83(1):22-28.

126. Koceja DM, Markus CA, Trimble MH. Postural modulation of the soleus H reflex in young and old subjects. Electroencephalogr Clin Neurophysiol 1995 Dec;97(6):387-393.

127. Baudry S, Lecoeuvre G, Duchateau J. Age-related changes in the behavior of the muscle-tendon unit of the gastrocnemius medialis during upright stance. J Appl Physiol (1985) 2012 Jan;112(2):296-304.

128. Baudry S, Penzer F, Duchateau J. Input-output characteristics of soleus homonymous Ia afferents and corticospinal pathways during upright standing differ between young and elderly adults. Acta Physiol (Oxf) 2014 Mar;210(3):667-677.

129. Klass M, Baudry S, Duchateau J. Modulation of reflex responses in activated ankle dorsiflexors differs in healthy young and elderly subjects. Eur J Appl Physiol 2011 Aug;111(8):1909-1916.

130. Shaffer SW, Harrison AL. Aging of the somatosensory system: a translational perspective. Phys Ther 2007 Feb;87(2):193-207.

131. Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP. Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. Neurosci Biobehav Rev 2009 Mar;33(3):271-278.

132. Jacobson BH, Thompson B, Wallace T, Brown L, Rial C. Independent static balance training contributes to increased stability and functional capacity in community-dwelling elderly people: a randomized controlled trial. Clin Rehabil 2011 Jun;25(6):549-556.

133. Halvarsson A, Franzen E, Faren E, Olsson E, Oddsson L, Stahle A. Long-term effects of new progressive group balance training for elderly people with increased risk of falling - a randomized controlled trial. Clin

Rehabil 2013 Oct 31;27:450-458.

134. Beck S, Taube W, Gruber M, Amtage F, Gollhofer A, Schubert M. Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. Brain Res 2007 Nov 7;1179:51-60.

135. Schubert M, Beck S, Taube W, Amtage F, Faist M, Gruber M. Balance training and ballistic strength training are associated with task-specific corticospinal adaptations. Eur J Neurosci 2008 Apr;27(8):2007-2018.

136. Taube W, Gruber M, Beck S, Faist M, Gollhofer A, Schubert M. Cortical and spinal adaptations induced by balance training: correlation between stance stability and corticospinal activation. Acta Physiol (Oxf) 2007 Apr;189(4):347-358.

137. Hufner K, Binetti C, Hamilton DA, Stephan T, Flanagin VL, Linn J, et al. Structural and functional plasticity of the hippocampal formation in professional dancers and slackliners. Hippocampus 2011 Aug;21(8):855-865.

138. Taubert M, Draganski B, Anwander A, Muller K, Horstmann A, Villringer A, et al. Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. J Neurosci 2010 Sep 1;30(35):11670-11677.

139. Taubert M, Lohmann G, Margulies DS, Villringer A, Ragert P. Long-term effects of motor training on resting-state networks and underlying brain structure. Neuroimage 2011 Aug 15;57(4):1492-1498.

140. Sehm B, Taubert M, Conde V, Weise D, Classen J, Dukart J, et al. Structural brain plasticity in Parkinson's disease induced by balance training. Neurobiol Aging 2014 Jan;35(1):232-239.

141. Burciu RG, Fritsche N, Granert O, Schmitz L, Sponemann N, Konczak J, et al. Brain changes associated with postural training in patients with cerebellar degeneration: a voxel-based morphometry study. J Neurosci 2013 Mar 6;33(10):4594-4604.

142. Mynark RG, Koceja DM. Down training of the elderly soleus H reflex with the use of a spinally induced balance perturbation. J Appl Physiol 2002 Jul;93(1):127-133.

143. Granacher U, Gollhofer A, Strass D. Training induced adaptations in characteristics of postural reflexes in elderly men. Gait Posture 2006 Dec;24(4):459-466.

144. Rovio S, Spulber G, Nieminen LJ, Niskanen E, Winblad B, Tuomilehto J, et al. The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol Aging 2010 Nov;31(11):1927-1936.

145. Talelli P, Waddingham W, Ewas A, Rothwell JC, Ward NS. The effect of age on task-related modulation of interhemispheric balance. Exp Brain Res 2008 Mar;186(1):59-66.

146. Hinder MR, Schmidt MW, Garry MI, Summers JJ. Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb. Exp Brain Res 2010 Sep;205(3):423-433.

147. Petitjean M, Ko JY. An age-related change in the ipsilateral silent period of a small hand muscle. Clin Neurophysiol 2013 Feb;124(2):346-353.

148. Hunter SK, Todd G, Butler JE, Gandevia SC, Taylor JL. Recovery from supraspinal fatigue is slowed in old adults after fatiguing maximal isometric contractions. J Appl Physiol 2008 Oct;105(4):1199-1209.

149. Eisen A, Entezari-Taher M, Stewart H. Cortical projections to spinal motoneurons: changes with aging and amyotrophic lateral sclerosis. Neurology 1996 May;46(5):1396-1404.

150. Lo YL, Fook-Chong S. A transcranial magnetic stimulation study of the ipsilateral silent period in lower

limb muscles. Neurosci Lett 2004 Sep 30;368(3):337-340.

CHAPTER 3

Age-related decrease in motor cortical inhibition during standing under different sensory conditions

S. Papegaaij

W. Taube

M. Hogenhout

S. Baudry

T. Hortobágyi

Frontiers in Aging Neuroscience 2014 June 12;6:126.

ABSTRACT

Background: Although recent studies point to the involvement of the primary motor cortex in postural control, it is unknown if age-related deterioration of postural control is associated with changes in motor cortical circuits. We examined the interaction between age and sensory condition in the excitability of intracortical motor pathways as indexed by short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) during standing. *Methods:* We used magnetic brain stimulation to evoke SICI and ICF in 11 young (range 21-25 years) and 12 healthy old adults (range 60-74 years) while they stood on a rigid platform or foam, with the eyes open or closed. *Results:* There was an overall age-related 43% reduction in SICI ($p = 0.001$). SICI lessened when standing on foam in old (31%) but not in young (1%) adults (condition × group interaction, $p = 0.049$). This reduction was associated with increases in center of pressure velocity ($r = -0.648$, $p = 0.043$). Age ($p = 0.527$) and sensory conditions ($p = 0.325$) did not affect ICF. *Conclusions:* Motor cortical circuits controlling leg muscles are modulated differently in healthy old vs. young adults during upright posture. Future experiments will clarify whether this difference mediates impaired postural control or serves as a compensatory mechanism to counteract postural instability.

1. INTRODUCTION

Accumulating evidence points to the involvement of the primary motor cortex (M1) in postural control [1-4]. Several studies also suggest that training of balance skills is associated with M1 plasticity [5,6] and that this plasticity correlates with improvements in postural control [7,8]. It is well known that postural control of upright stance progressively declines with age. Many factors have been identified to contribute to the age-related deterioration of postural control, including reduced muscle strength [9], impaired sensory abilities [10], slowed nerve conduction velocity [11], and altered spinal reflexes [12,13]. In addition, the excitability of the corticospinal pathway, including the direct projections (monosynaptic) from cortical neurons to spinal motor neurons, is greater in old compared with young adults during upright standing [14,15]. It is unknown if, in addition to age-related changes in the corticospinal pathway, aging also influences intracortical circuits during upright standing.

During manual motor tasks, neuroimaging studies report greater activation in M1, premotor, and prefrontal areas in old compared with young adults [16-18]. Similarly, studies using transcranial magnetic stimulation (TMS) revealed disinhibition in several M1 inhibitory circuits in old compared with young adults during manual motor tasks, as reflected by decreases in interhemispheric inhibition, silent period, cortical reciprocal inhibition, and short-interval intracortical inhibition [19-24]. However, several other studies report no changes [20,25] or even increased inhibition with age [26,27]. These inconsistencies in literature are probably related to differences in task difficulty, age range and the type of muscle examined. Age-related decreases in intracortical inhibition have been associated with worse motor performance measured under a variety of experimental conditions [19,22,23]. Thus, there is ample evidence that aging modifies intracortical processing and that such modifications can affect motor control [28]. Hence, it seems reasonable to expect that age-related changes in intracortical circuits are – at least in part – responsible for the deterioration in postural control.

Therefore, the purpose of the present study was to examine the interaction between age and sensory condition in M1 excitability as indexed by short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) during standing. We manipulated sensory condition by altering proprioceptive feedback (standing on a rigid platform vs. foam) and visual feedback (eyes open vs. eyes closed).

Based on work showing modulations in inhibitory spinal circuits with sensory conditions and postural task difficulty [12,13,29], we hypothesized that behaviorally relevant modulations would also occur in M1 excitability. Specifically, we expected a reduction of SICI with altered sensory conditions, to increase M1 excitability and consequently the number of motor solutions available. In addition, based on the previously mentioned studies reporting cortical disinhibition with aging [19-24], we expected that old adults would show a generally reduced SICI compared to

young adults. Based on the findings of Heise et al. [23], we hypothesized that this age-related disinhibition during normal standing would result in a decreased modulation of SICI between tasks. To validate the putative role of M1 in postural control, we predicted an association between the task-related modulation of M1 excitability and alteration in postural stability. Because of a lack of data concerning ICF modulation during postural tasks, the formulation of a specific hypothesis is premature.

2. METHODS

2.1. Participants

Eleven healthy young adults (age 23 ±1 years, range 21-25 years, 4 men) and fourteen healthy old adults (age 68 ±5 years, range 60-77 years, 11 men) volunteered for the study. In two old men (age 66 and 77 years) the stimulation intensity was above the comfort threshold and we stopped data collection. Two young and two old adults were left-footed [30]. None of the participants had a history of or presented with neurological disorders, severe orthopedic disorders, suspicion of pregnancy, non-dental associated metal within the cranium, or took neuroactive drugs or drugs known to affect balance. The mini-mental state examination (MMSE) and short questionnaire to assess health-enhancing physical activity (SQUASH) were used to determine general cognitive function and physical activity in daily life. Subjects also completed the short physical performance battery (SPPB) including standing balance, walking speed and chair stand tests to specifically evaluate lower extremity function (Table 1). Before the experiment, subjects signed an informed consent document approved by the Medical Ethics Committee of the University Medical Center Groningen.

2.2. Experimental setup

Surface electromyography (EMG) was recorded (DE-2.1, Delsys, Natick, MA, USA) for the right tibialis anterior (TA) by attaching active electrodes over the muscle belly and the reference electrode on the medial aspect of the tibia. To minimize impedance at the electrode-skin contact, the skin was shaven, abraded with fine-grain sandpaper, and cleaned with alcohol. The EMG signal was amplified 1000 times (model Bagnoli-8, Delsys, Natick, MA, USA), sampled at 5 kHz, and band-pass filtered with a second order Butterworth filter (10-1000 Hz) using data acquisition interface and software (Power 1401 and Spike2, Cambridge Electronics Design, Cambridge, UK). Subjects performed a maximum voluntary contraction (MVC) of the ankle dorsal flexors while seated in a chair with the knee in 45° flexion and the ankle in neutral position. The EMG activity recorded during this effort was used to express and normalize the background EMG.

During the main part of the experiment, subjects were instructed to maintain an upright bipedal stance on two force plates (Bertec 4060-08, Columbus, OH, USA). With the arms crossed

Table 1. Subject characteristics.

	Young adults	Old adults
Age (years)	23 ± 1	68 ± 4
Sex (male; female)	4; 7	11; 3
BMI (kg/m^2)	23 ± 1.7	24 ± 3.6
SPPB score	12 ± 0	12 ± 1
MMSE score	30 ± 0	30 ± 1
SQUASH		
- total score	9718 ± 1934	10045 ± 3236
- light (min/w)	2337 ± 580	912 ± 829
- moderate (min/w)	459 ± 309	353 ± 284
- heavy (min/w)	222 ± 229	602 ± 218

Values are mean ± SD, unless indicated differently. BMI: body mass index, SPPB: short physical performance battery (max. score of 12), MMSE: mini mental state examination (max. score of 30), SQUASH: short questionnaire to assess health-enhancing physical activity. Total score is minutes per week × intensity of the activity. The amount of light, moderate and heavy exercise is expressed in minutes per week.

across the chest, subjects looked at a sharply visible "+" sign displayed on a projection screen.

Foot position was standardized with the heels 9 cm apart and a toe-out angle of 30°. The center of pressure (CoP) position signal was sampled at 100 Hz, and filtered using a fourth order low-pass Butterworth filter with a cut off frequency of 10 Hz. It was not necessary to correct the CoP position data for height of the foam (6 cm) because pilot experiments showed a minimal effect.

An 11-video-camera motion analysis system (Vicon, Oxford, UK) recorded spatial coordinates of reflective markers placed on the right trochanter major and lateral malleolus. The signal was sampled at 100 Hz, filtered with a second order low-pass Butterworth filter (cut off frequency: 5 Hz), and used online to determine whether the person was swaying forward or backward.

In a random order, subjects performed four standing conditions with altered sensory states: standing on a rigid surface with eyes open (rigid – EO) and eyes closed (rigid – EC), standing on foam (47 cm × 38 cm × 6 cm, Bodybow Healthcare BV, Nieuwegein, Netherlands) with eyes open (foam – EO) and eyes closed (foam – EC). Three minute resting periods were given between conditions to prevent fatigue. We also recorded two periods of 10 s per surface condition (rigid, foam) where participants assumed the standardized position without receiving TMS.

2.3. TMS data acquisition

In the present study, transcranial magnetic stimuli were delivered over the left M1 with a double cone coil connected to a Magstim 200^2 and Bistim^2 (Magstim, Whitland, UK), except for two old

adults for whom a 90 mm circular coil was used as no clear MEP was evoked with the double-cone coil. We targeted the TA because this muscle generally provides a low motor threshold (MT) and good reliability of MEPs [31]. The optimal location for eliciting MEP's in the TA with the largest amplitude at a given intensity was determined by moving the coil systematically in steps of 0.5 cm over the M1 area starting at the vertex. In general, the optimal location was found 0.5-1.5 cm posterior and lateral to the vertex. The location was marked on the skull with a permanent marker to enable the experimenter to hold the coil on a consistent location throughout the experiment. While standing, the MT, defined as the lowest intensity in which the MEP's were larger than 100 μV in at least three out of five consecutive trials, was determined [17].

Paired-pulse TMS with an interstimulus interval of 2.5 ms was used to assess SICI, while an interstimulus interval of 13 ms was used to assess ICF. The interstimulus intervals were chosen based on the literature [32,33] and pilot experiments showing greatest inhibition and facilitation at these intervals. Conditioning and test stimulation intensity were set at 0.8 and 1.2 MT, respectively. In all standing conditions there were 10 test MEP, 10 SICI and 10 ICF trials. To reduce variability in MEP size induced by sway direction [2] and to minimize the magnitude of background EMG, TMS was triggered only when the person was swaying forward (negative angular velocity) and with a minimal interval of 5 s between trials.

2.4. Data analysis

Rectified background EMG was averaged in each trial over the 100-ms period preceding the TMS artifact, and expressed as a percentage of the EMG activity measured during the MVC trial. The peak-to-peak amplitude of the TMS-generated MEPs was computed. Using the interquartile range [34], four percent of the total number of trials were identified as outliers and were substituted with the mean. SICI and ICF were expressed as percentage inhibition and facilitation, by using the following formula for SICI: 100 - (conditioned MEP/test MEP × 100), and the following formula for ICF: (conditioned MEP/test MEP × 100) - 100. CoP velocity while standing on the rigid platform and on foam was used to describe the postural behavior of subjects. CoP velocity is a highly reliable measure [35] that has proven to discriminate well between age groups and test situations [36].

2.5. Statistical analyses

All variables were checked for normal distribution prior to analysis. Background EMG was logarithmically transformed because of a skewed distribution. We compared MT between young and old adults using an independent samples t-test. The main analysis was an Age (young, old) by Condition (rigid-EO, rigid-EC, foam-EO, foam-EC) two-way repeated measures ANOVA on test MEP amplitude, SICI, ICF and background EMG. In case of a significant condition effect, results

were subjected to a post hoc Tukey's test. Because CoP velocity was only measured in two conditions (rigid, foam), this outcome measure was analyzed in an Age (young, old) by Condition (rigid, foam) two-way repeated measures ANOVA. A Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. Pearson correlation coefficients were computed to assess the association of background EMG with test MEP amplitude, SICI and ICF, and the association of test MEP amplitude with SICI, using the combined age group data. Furthermore, Pearson correlation coefficients were computed to examine the relationship between the changes in SICI and CoP velocity from rigid to foam conditions in the two age groups. IBM SPSS statistics 20 was used for statistical analysis. The alpha level was set at 0.05. Results are presented as mean ± SD in the text and tables and mean ± SE in Figures 1 and 3. Interaction effects are only reported when significant.

3. RESULTS

3.1. Center of pressure

There was a significant age × condition interaction effect for CoP velocity ($F_{1,19}$ = 15.8; p = 0.001) (Figure 1), with a greater increase in CoP velocity from the rigid to the foam condition in old adults (from 1.75 to 2.58 cm/s, p < 0.001) as compared to young adults (from 1.54 to 1.85 cm/s, p < 0.001).

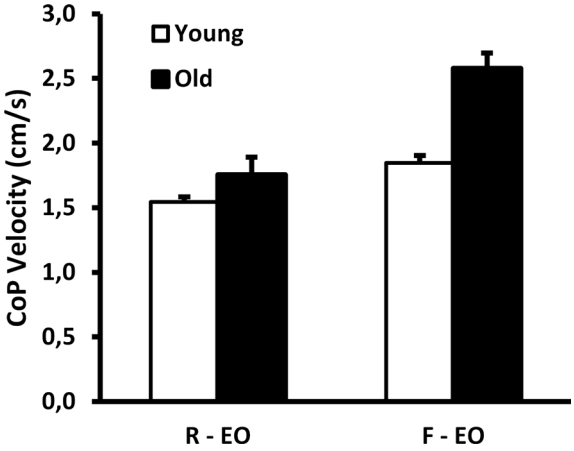


Figure 1 | Group data (mean ± SE) for young and old adults of center of pressure velocity when standing on a rigid surface and on foam, showing a significant interaction effect (p = 0.001) EO: eyes open.

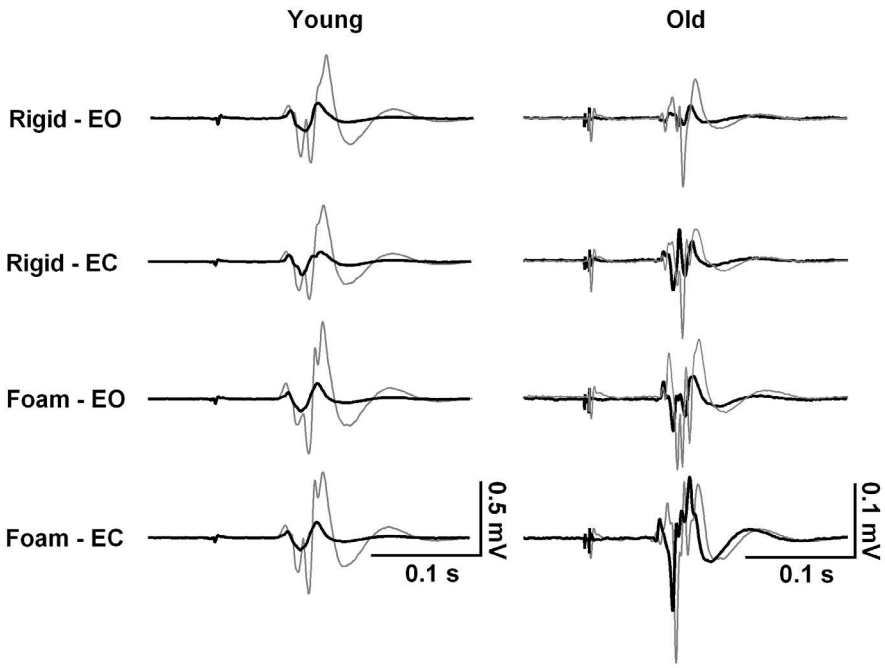


Figure 2 | Representative responses to transcranial magnetic brain stimulation in the tibialis anterior muscle of one 23-year-old female and one 73-year-old male participant while standing on rigid and foam surfaces with eyes open (EO) and eyes closed (EC). Waveforms represent the motor evoked potential averaged over ten trials in response to an unconditioned test pulse (thing grey line) and to a conditioned test pulse (thick black line) at 2.5 milliseconds interval. Note the absence of modulation of short interval intracortical inhibition (SICI) across the four conditions in the young subject, in contrast to the old subject who decreases SICI when sensory conditions are altered.

3.2. TMS measures

Across all subjects, MT was similar in young (49 ± 8%, range 34 – 55%) and old adults (50 ± 12%, range 31 – 73%, t_{21} = -0.2, p = 0.845). Therefore, the average stimulation intensities were similar in the two age groups. The effects of sensory condition on TMS responses from a representative young and old subject are illustrated in Figure 2. Group data show that test MEP amplitude was similar in young and old adults ($F_{1,20}$ = 1.3, p = 0.261) (Figure 3A). However, there was a significant condition effect ($F_{2,39}$ = 14.2, p < 0.001). Post hoc tests revealed that the test MEP's during standing on foam were greater compared with those recorded while standing on a rigid surface (p < 0.01), and during foam-EC compared with foam-EO (p < 0.001). However, no difference related to vision conditions was observed when standing on a rigid surface (p>0.05). The 2 × 4 ANOVA did not reveal significant modulation between conditions for SICI ($F_{3,60}$ = 1.7, p = 0.185), but SICI was greater in young adults (67 ± 23%) compared to old adults (39 ± 20%) regardless of

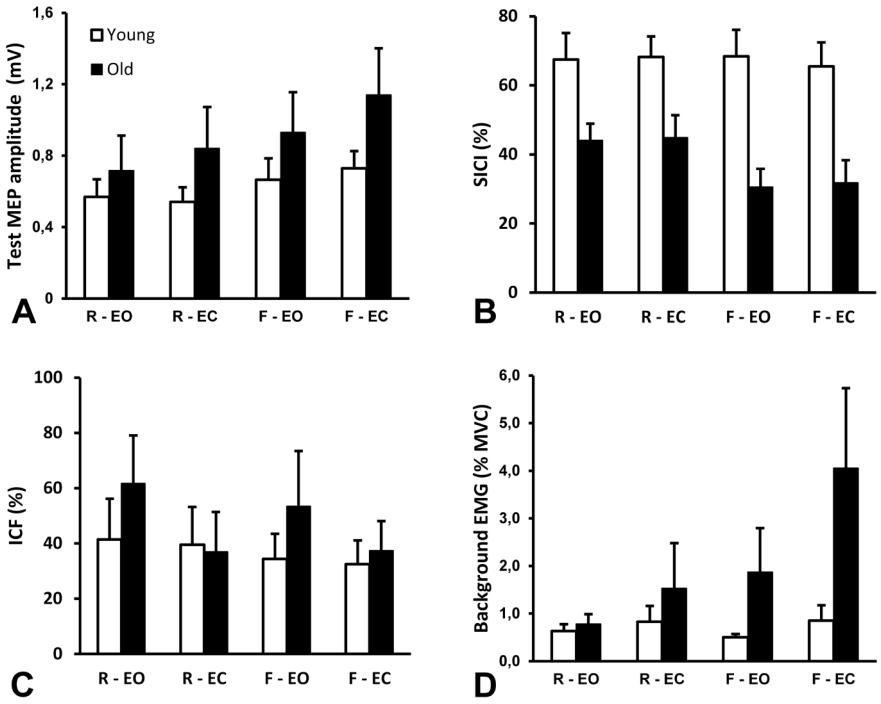


Figure 3 | Group data (mean ± SE) for young and old adults of (**A**) amplitude test MEP (condition effect, $p < 0.001$), (**B**) short interval intracortical inhibition (SICI) (group effect, $p = 0.001$; interaction effect, $p = 0.049$), (**C**) intracortical facilitation (ICF), (**D**) background EMG (interaction effect, $p = 0.031$). Conditions were standing on a rigid platform and on foam (rigid, foam), with eyes open and eyes closed (EO, EC). Greater values for SICI and ICF represent respectively more inhibition and facilitation.

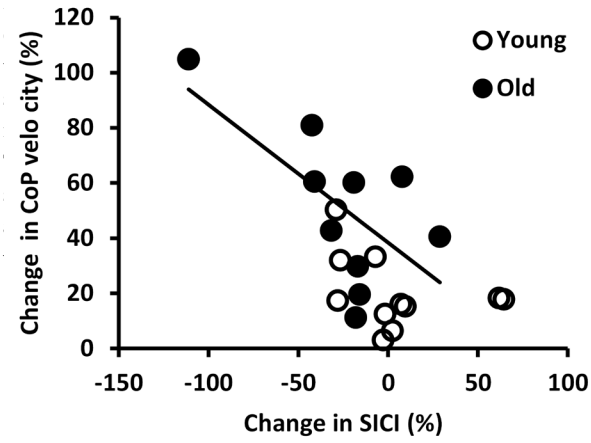


Figure 4. Correlation between the percent changes in short interval intracortical inhibition (SICI) and center of pressure (CoP) velocity from the rigid to the foam condition in young and old adults. The regression line illustrates that in old subjects greater reductions in SICI were accompanied by greater increases in CoP velocity ($r = -0.648$, $p = 0.043$).

standing condition ($F_{1,20}$ = 16.5, p = 0.001) (Figure 3B). Furthermore, when pooled across vision conditions, the 2 (young, old) by 2 (rigid, foam) ANOVA revealed a significant age × condition interaction ($F_{1,20}$ = 4.4, p = 0.049), with a decrease in SICI from rigid to foam in old (31% change, p < 0.001) but not in young adults (p > 0.05). Age and conditions did not affect ICF ($F_{1,20}$ = 0.4, p = 0.527; $F_{3,60}$ = 1.2, p = 0.325) (Figure 3C).

3.3. Background EMG

Figure 3D shows the group × condition interaction ($F_{2,34}$ = 4.1; p = 0.031) for the log-transformed background EMG in the TA, with a greater increase in background EMG when altering the sensory conditions in old compared to young adults. Post hoc tests revealed that there was no effect of sensory condition on background EMG in young adults (p > 0.05). In old adults all comparisons between conditions were significant (p < 0.05), except for rigid-EO vs. rigid-EC (p > 0.05). Moreover, bEMG did not differ between age groups during the rigid surface conditions (p > 0.05), but was higher in old adults during the foam surface conditions (p < 0.001).

3.4. Correlations

To determine whether differences in background EMG could have caused the condition (rigid vs. foam) and age (young vs. old) effects in TMS measures, we performed correlation analyses. The changes in background EMG between the rigid and the foam conditions did not correlate signifi cantly with the changes in test MEP amplitude (r = 0.27, p = 0.244), SICI (r = -0.29, p = 0.202) or ICF (r = -0.25, p = 0.275). Furthermore, there was no significant correlation between the changes in test MEP amplitude and SICI (r = -0.26, p = 0.239) or ICF (r = -0.17, p = 0.444).

Figure 4 shows the relationship between changes in SICI and CoP velocity from the rigid to the foam condition in young and old adults. Within the old adults, subjects who reduced their SICI more when changing from standing on a rigid surface to standing on the foam, showed a greater increase in CoP velocity (r = -0.65, p = 0.043).

4. DISCUSSION

This is the first study that examines the effects of age on intracortical circuit excitability during postural tasks. The data confirmed the overriding hypothesis of an interaction between age and sensory condition in M1 excitability: SICI lessened when standing on foam compared with standing on a rigid surface in old but not in young adults. This reduction was associated with a greater decrease in stability when the support surface was altered. In contrast, ICF did not vary with age and sensory conditions. This study extends the literature reporting on the age-related reductions in cortical inhibition during manual tasks by demonstrating similar reductions in cortical inhibition during a postural task.

4.1. Age-related decrease in SICI

Previous studies reported inconsistent results concerning the association between age and SICI. The inconsistencies may in part be due to differences in the strength of corticomotoneuronal projections to the target muscle. For example, hand muscles compared with forearm muscles have more abundant monosynaptic projections [37], and SICI investigated in motor cortex associated with hand muscles has been reported to be reduced [22,23] or similar [20,25] in old compared with young adults. In contrast, studies examining wrist flexors and extensors found more SICI in old than in young adults [26,27]. As the TA exhibits nearly similar density of corticospinal projections as hand muscles [38,39], results of the present study support the hypothesis of a specific reduction in SICI for muscles with rich corticospinal projections, suggesting that aging further strengthens the corticomotoneuronal pathway by diminishing intracortical inhibition. Nonetheless, this may also reflect a greater contribution of this pathway during upright standing, regardless of leg muscles (Baudry et al. 2014b).

4.2. Posture-specific reductions in SICI affect performance

In addition to the lower SICI in elderly adults, the present results show that elderly adults modulated SICI depending on the sensory conditions, and more specifically the surface of support. There are several studies showing changes in SICI related to motor control. For example, SICI is reduced during movement preparation [23], during the activation phase compared with the deactivation phase in cycling [40], and after periods of motor practice [41,42]. However, we found no difference in SICI between tasks in young adults, resulting in a significant age × condition interaction. It must be noted that this interaction was only significant when data was pooled across vision conditions, probably due to a relatively low number of participants. Also, this might indicate that the modulation only occurs when balance is truly challenged, as changing the surface usually has a bigger impact than removing vision [12]. The lack of modulation in SICI in young adults is in line with a previous study that reported similar SICI levels during voluntary and postural contraction of the soleus muscle, suggesting that SICI is not specifically modulated during upright standing in young adults [32]. This may be because increasing M1 excitability would not improve muscle coordination needed to perform a difficult postural task. It may also be that the postural tasks were not challenging enough for the young adults to require changes in neural control, although young adults did increase CoP velocity when standing on foam.

Nonetheless, old adults exhibited a lower level of SICI when standing on foam compared to standing on a rigid surface. Within the group of old adults, reduction in SICI correlated with increase in CoP velocity. This is consistent with other studies reporting a correlation between low intracortical inhibition and poor motor performance in old adults [19,22,23]. Lower SICI was associated with poorer performance in the Purdue Pegboard test for manual dexterity, but not

with performance on a pinch grip force control task [22]. The correlation was driven by a number of (primarily old) subjects who exhibited atypically low inhibition, appearing as facilitation. There was also an association between the strength of intracortical inhibition measured by the contralateral silent period during an interlimb coordination task and the performance on this task [19]. At last, there was a link between the level of SICI at rest and single reaction time and two finger tapping speed [23]. Although all three papers [19,22,23] found an association between age-related disinhibition and reductions in motor performance, these studies did not quantify changes between tasks, instead reported inhibition only during one specific task [19,22] or at rest [23]. Therefore, the present study is the first to show that task-related modulation in SICI can be linked to behavior in old adults. One interpretation could be that the task-specific reduction in SICI was dysfunctional, negatively affecting postural control. As phasic activation of GABA-A receptors is thought to contribute to the regulation of synchronous motor neuronal activity [43], it is suggested that a general disinhibition could interfere with this process [23], and therefore induce difficulties when one is required to coordinate the fast contractions of different muscles during standing on foam.

However, we cannot exclude the possibility that the reduction in SICI in old adults was a compensatory mechanism. It can be argued that standing on foam is a relatively more difficult task for old than young subjects, and that the more subjects were challenged the more they were 'forced' to facilitate M1 activity. Therefore, neither the previous nor the current data can determine whether increased instability caused reduced SICI or the other way around.

4.3. No age-related changes in ICF

We did not find differences in ICF between young and old adults, which is consistent with two studies that examined ICF in the first dorsal interosseus muscle [25,44]. However, it is inconsistent with two other studies that reported lower ICF in the wrist flexors and extensors of old compared with young adults [26,27]. This is in line with the earlier proposed shift towards an age-related facilitation of the muscles with strong corticospinal projections. Given the decrease in SICI, the lack of change in ICF may indicate that modulation of cortical circuits with sensory conditions relies more on reducing strength of inhibitory inputs to increase the potential for more cortical contribution to control leg muscles rather than increasing cortical activity. This is in agreement with the lack of changes in test MEP observed in the present study and the absence of modulation in corticomotoneural excitability with altered proprioception [14]. Such adjustments may be relevant to increase the cortical contribution to postural control without increasing cortical activity that may induce noisy neural signal.

Although many studies have used ICF to investigate cortical excitability [32,42,45,46], the neurophysiological origin of ICF is still under debate [47]. As N-methyl-d-aspartate (NMDA) receptor antagonists and glutamate antagonists decrease ICF, it is often believed to reflect glutami-

nergic intracortical circuits [48,49]. However, there is some evidence that GABAergic inhibition can modulate ICF [50]. Furthermore, spinal contributions cannot be excluded [51]. Therefore, conclusions regarding ICF should be used with caution, and short interval intracortical facilitation (SICF), an often overlooked measure, might actually be more valid for determining cortical facilitation [52,53].

4.4. The influence of background EMG

One limitation of this study is the difference in background EMG between conditions and groups. Since the level of muscle contraction could affect SICI, this might have influenced the results. However, there are several reasons why we think this is not the case. First, the contractions were of very low intensity, with an average of 0.9 and 4.1% of MVC in young and old adults during the most difficult condition. Second, the age-related decrease in SICI was also apparent in the rigid-EO condition, while the background EMG did not differ between groups in that condition. Third, the modulation between conditions in SICI did not correlate with the modulation of background EMG.

4.5. Future recommendations and conclusions

Future studies are needed to better understand the cause-effect relationship between SICI and postural control in aging. One aspect in these studies could be to test the hypothesis of an interaction between age and the strength of corticospinal projection to the target muscle on the amount of SICI and ICF by targeting several muscles. If this proves to be true, such data would address many inconsistencies reported in literature and provide a deeper insight into the age-related changes of the neuromotor system. Another aspect could be the association between behavioral and neurophysiological changes after balance training.

In conclusion, old compared with young adults exhibited an overall decreased level of SICI and reduced this even further when standing with altered proprioception. The reduction in SICI between tasks was associated with an increased velocity of the CoP. This suggests that motor cortical circuits control upright posture differently in old vs. young adults. Future experiments will clarify whether this difference in control mediates impaired postural control or serves as a compensatory mechanism to counteract postural instability.

REFERENCES

1. Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A. Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. J Appl Physiol 2006 Aug;101(2):420-429.

2. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of human standing. Acta Physiol (Oxf) 2009 Mar;195(3):385-395.

3. Taube W, Gruber M, Gollhofer A. Spinal and supraspinal adaptations associated with balance training and

their functional relevance. Acta Physiol (Oxf) 2008 Jun;193(2):101-116.

4. Beloozerova IN, Sirota MG, Swadlow HA, Orlovsky GN, Popova LB, Deliagina TG. Activity of different classes of neurons of the motor cortex during postural corrections. J Neurosci 2003 Aug 27;23(21):7844-7853.

5. Beck S, Taube W, Gruber M, Amtage F, Gollhofer A, Schubert M. Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. Brain Res 2007 Nov 7;1179:51-60.

6. Schubert M, Beck S, Taube W, Amtage F, Faist M, Gruber M. Balance training and ballistic strength training are associated with task-specific corticospinal adaptations. Eur J Neurosci 2008 Apr;27(8):2007-2018.

7. Taube W, Gruber M, Beck S, Faist M, Gollhofer A, Schubert M. Cortical and spinal adaptations induced by balance training: correlation between stance stability and corticospinal activation. Acta Physiol (Oxf) 2007 Apr;189(4):347-358.

8. Taubert M, Draganski B, Anwander A, Muller K, Horstmann A, Villringer A, et al. Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. J Neurosci 2010 Sep 1;30(35):11670-11677.

9. Boelens C, Hekman EE, Verkerke GJ. Risk factors for falls of older citizens. Technol Health Care 2013;21(5):521-533.

10. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. Physiol Rev 2012 Oct;92(4):1651-1697.

11. Nardone A, Siliotto R, Grasso M, Schieppati M. Influence of aging on leg muscle reflex responses to stance perturbation. Arch Phys Med Rehabil 1995 Feb;76(2):158-165.

12. Baudry S, Duchateau J. Age-related influence of vision and proprioception on Ia presynaptic inhibition in soleus muscle during upright stance. J Physiol 2012 Nov 1;590(Pt 21):5541-5554.

13. Koceja DM, Markus CA, Trimble MH. Postural modulation of the soleus H reflex in young and old subjects. Electroencephalogr Clin Neurophysiol 1995 Dec;97(6):387-393.

14. Baudry S, Penzer F, Duchateau J. Vision and proprioception do not influence the excitability of the corticomotoneuronal pathway during upright standing in young and elderly adults. Neuroscience 2014 May 30;268:247-254.

15. Baudry S, Penzer F, Duchateau J. Input-output characteristics of soleus homonymous Ia afferents and corticospinal pathways during upright standing differ between young and elderly adults. Acta Physiol (Oxf) 2014 Mar;210(3):667-677.

16. Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. Brain 2003 Apr;126(Pt 4):873-888.

17. Calautti C, Serrati C, Baron JC. Effects of age on brain activation during auditory-cued thumb-to-index opposition: A positron emission tomography study. Stroke 2001 Jan;32(1):139-146.

18. Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002 Feb 26;58(4):630-635.

19. Fujiyama H, Hinder MR, Schmidt MW, Garry MI, Summers JJ. Age-related differences in corticospinal excitability and inhibition during coordination of upper and lower limbs. Neurobiol Aging 2012 Jul;33(7):1484.e1-1484.14.

20. Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, et al. Effects of aging on motor cortex excit-

ability. Neurosci Res 2006 May;55(1):74-77.

21. Hortobagyi T, del Olmo MF, Rothwell JC. Age reduces cortical reciprocal inhibition in humans. Exp Brain Res 2006 May;171(3):322-329.

22. Marneweck M, Loftus A, Hammond G. Short-interval intracortical inhibition and manual dexterity in healthy aging. Neurosci Res 2011 Aug;70(4):408-414.

23. Heise KF, Zimerman M, Hoppe J, Gerloff C, Wegscheider K, Hummel FC. The Aging Motor System as a Model for Plastic Changes of GABA-Mediated Intracortical Inhibition and Their Behavioral Relevance. J Neurosci 2013 May 22;33(21):9039-9049.

24. Talelli P, Waddingham W, Ewas A, Rothwell JC, Ward NS. The effect of age on task-related modulation of interhemispheric balance. Exp Brain Res 2008 Mar;186(1):59-66.

25. Smith AE, Ridding MC, Higgins RD, Wittert GA, Pitcher JB. Cutaneous afferent input does not modulate motor intracortical inhibition in ageing men. Eur J Neurosci 2011 Nov;34(9):1461-1469.

26. Kossev AR, Schrader C, Dauper J, Dengler R, Rollnik JD. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. Neurosci Lett 2002 Nov 22;333(2):83-86.

27. McGinley M, Hoffman RL, Russ DW, Thomas JS, Clark BC. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. Exp Gerontol 2010 Sep;45(9):671-678.

28. Papegaaij S, Taube W, Baudry S, Otten E, Hortobagyi T. Aging causes a reorganization of cortical and spinal control of posture. Front Aging Neurosci 2014 Mar 3;6:28.

29. Katz R, Meunier S, Pierrot-Deseilligny E. Changes in presynaptic inhibition of Ia fibres in man while standing. Brain 1988 Apr;111(Pt 2):417-437.

30. Hebbal GV, Mysorekar VR. Evaluation of some tasks used for specifying handedness and footedness. Percept Mot Skills 2006 Feb;102(1):163-164.

31. Cacchio A, Cimini N, Alosi P, Santilli V, Marrelli A. Reliability of transcranial magnetic stimulation-related measurements of tibialis anterior muscle in healthy subjects. Clin Neurophysiol 2009 Feb;120(2):414-419.

32. Soto O, Valls-Sole J, Shanahan P, Rothwell J. Reduction of intracortical inhibition in soleus muscle during postural activity. J Neurophysiol 2006 Oct;96(4):1711-1717.

33. Roshan L, Paradiso GO, Chen R. Two phases of short-interval intracortical inhibition. Exp Brain Res 2003 Aug;151(3):330-337.

34. Tukey JW. Exploratory Data Analysis. : Addison-Wesley; 1977.

35. Demura S, Kitabayashi T, Aoki H. Body-sway characteristics during a static upright posture in the elderly. Geriatr Gerontol Int 2008 Sep;8(3):188-197.

36. Raymakers JA, Samson MM, Verhaar HJ. The assessment of body sway and the choice of the stability parameter(s). Gait Posture 2005 Jan;21(1):48-58.

37. Palmer E, Ashby P. Corticospinal projections to upper limb motoneurones in humans. J Physiol 1992 Mar;448:397-412.

38. Petersen NT, Pyndt HS, Nielsen JB. Investigating human motor control by transcranial magnetic stimulation. Exp Brain Res 2003 Sep;152(1):1-16.

39. Brouwer B, Ashby P. Corticospinal projections to lower limb motoneurons in man. Exp Brain Res 1992;89(3):649-654.

40. Sidhu SK, Cresswell AG, Carroll TJ. Short-interval intracortical inhibition in knee extensors during locomotor cycling. Acta Physiol (Oxf) 2013 Jan;207(1):194-201.

41. Rosenkranz K, Kacar A, Rothwell JC. Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. J Neurosci 2007 Oct 31;27(44):12058-12066.

42. Smyth C, Summers JJ, Garry MI. Differences in motor learning success are associated with differences in M1 excitability. Hum Mov Sci 2010 Oct;29(5):618-630.

43. Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. Nat Rev Neurosci 2005 Mar;6(3):215-229.

44. Smith AE, Ridding MC, Higgins RD, Wittert GA, Pitcher JB. Age-related changes in short-latency motor cortex inhibition. Exp Brain Res 2009 Oct;198(4):489-500.

45. Howatson G, Taylor MB, Rider P, Motawar BR, McNally MP, Solnik S, et al. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. Eur J Neurosci 2011 Mar;33(5):978-990.

46. Ginanneschi F, Del Santo F, Dominici F, Gelli F, Mazzocchio R, Rossi A. Changes in corticomotor excitability of hand muscles in relation to static shoulder positions. Exp Brain Res 2005 Mar;161(3):374-382.

47. Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 2008 Jan 15;586(2):325-351.

48. Ziemann U, Chen R, Cohen LG, Hallett M. Dextromethorphan decreases the excitability of the human motor cortex. Neurology 1998 Nov;51(5):1320-1324.

49. Liepert J, Schwenkreis P, Tegenthoff M, Malin JP. The glutamate antagonist riluzole suppresses intracortical facilitation. J Neural Transm 1997;104(11-12):1207-1214.

50. Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 1996 Apr;109(1):127-135.

51. Di Lazzaro V, Pilato F, Oliviero A, Dileone M, Saturno E, Mazzone P, et al. Origin of facilitation of motor-evoked potentials after paired magnetic stimulation: direct recording of epidural activity in conscious humans. J Neurophysiol 2006 Oct;96(4):1765-1771.

52. Di Lazzaro V, Rothwell JC, Oliviero A, Profice P, Insola A, Mazzone P, et al. Intracortical origin of the short latency facilitation produced by pairs of threshold magnetic stimuli applied to human motor cortex. Exp Brain Res 1999 Dec;129(4):494-499.

53. Clark J, Loftus A, Hammond G. Age-related changes in short-interval intracortical facilitation and dexterity. Neuroreport 2011 Jul 13;22(10):499-503.

CHAPTER 4

Intracortical inhibition in the soleus muscle is reduced during the control of upright standing in both young and old adults

S. Papegaaij

S. Baudry

J. Négyesi

W. Taube

T. Hortobágyi

European Journal of Applied Phyisology 2015: Under review.

ABSTRACT

Purpose: In a previous study, we reported that short-interval intracortical inhibition (SICI) decreases in old but not in young adults when standing on foam vs. standing on a rigid surface. Here, we examined if such an age by task difficulty interaction in motor cortical excitability also occurs in easier standing tasks. *Methods:* Fourteen young (23 ± 2.7 years) and fourteen old (65 ± 4.1 years) adults received transcranial magnetic brain stimulation and peripheral nerve stimulation while they stood with or without support on a force platform. *Results:* In the soleus, we found that SICI was lower in unsupported (35% inhibition) vs. supported (50%) standing ($p = 0.007$) but similar in young vs. old adults ($p = 0.591$). In the tibialis anterior, SICI was similar between conditions ($p = 0.597$) but lower in old (52%) vs. young (72%) adults ($p = 0.030$). Age and standing with or without support did not affect the Hoffmann reflex in the soleus. *Conclusions:* Overall, past and current data suggests that the motor cortex is involved in standing control and that its role becomes more prominent with an increase in task difficulty and age.

1. INTRODUCTION

An increasing body of literature supports the notion that the primary motor cortex (M1) is involved in the control of upright standing. For example, M1 excitability in the tibialis anterior and soleus is higher during normal compared with supported standing [1]. Moreover, the amount of short interval intracortical inhibition (SICI), that likely reflects the excitability of GABAergic inhibitory intracortical circuits [2], is similar during a voluntary contraction of the soleus muscle while sitting and a postural contraction while standing [3]. The involvement of M1 in balance control in young adults is further supported by the increase in corticomotoneuronal excitability in the soleus muscle after backwards surface translation [4].

Recent studies reported an age-related increase in corticospinal excitability in the soleus muscle during the control of upright standing [5,6]. This increase is accompanied by a decreased efficacy of Ia afferents to discharge spinal motor neurons [6-8]. These results imply an age-related increase in cortical contribution to control leg muscles during standing. Indeed, aging seems to influence the modulation of intracortical pathways, as indicated by the decrease in SICI from standing on a rigid surface to an unstable surface (foam mat) in old but not in young adults [9]. This reduction in SICI between balance tasks was associated with an increased center of pressure (CoP) velocity, highlighting the importance of intracortical circuits in controlling standing. An age-related increase in cortical control of standing could reflect a functional compensation for structural degeneration in the peripheral and central nervous system, increasing the need for a more adaptable control system.

The age-related difference in SICI modulation may be due to different motor control strategies between young and old. However, it may also be due to the task, i.e., standing on unstable surface, being more difficult for old than for young adults [9]. Therefore, our goal was to determine if there is also an age-related difference in the modulation of intracortical and spinal circuits during relatively simple balance tasks. Subjects stood naturally upright (unsupported standing) or while lightly touching a board at chest level (supported standing) to remove the need for the nervous system to control body sway. To examine SICI and intracortical facilitation (ICF), paired pulse transcranial magnetic stimulation (TMS) was applied during the two conditions. To examine the efficacy of Ia afferents to activate spinal motor neurons, peripheral nerve stimulation was used.

We hypothesized an age-related decrease in SICI and a down modulation in SICI when standing unsupported vs. supported in old but not in young adults [9]. In contrast, we expected no age- or condition-related changes in ICF [9]. Based on previous data, we hypothesized greater down modulation of the Hoffmann reflex (H-reflex) from supported to unsupported standing in old compared with young adults [1,6].

2. MATERIALS AND METHODS

2.1. Participants

Twenty young adults and nineteen old adults volunteered for the study. In six young and five old adults we stopped TMS data collection because the stimulation intensity was above comfort threshold. For the peripheral nerve stimulation (PNS), there were two young adults and four old adults in whom we could not evoke an H-reflex in the soleus. Therefore, TMS data from fourteen young (age 23 ± 2.7 years, range 18-29, 9 men) and fourteen old (age 65 ± 4.1 years, range 60-76, 8 men) adults and PNS data from eighteen young (age 23 ± 2.8 years, range 18-29, 9 men) and sixteen old (age 65 ± 4.1 years, range 60-76, 8 men) adults were used in the statistical analyses. Subject characteristics were similar between those who finished and did not finish the experiments. Four young and one old subject were left-footed. None of the subjects had a history of or presented with neurological disorders, severe orthopedic disorders, suspicion of pregnancy, non-dental associated metal within the cranium, or took neuroactive drugs or drugs known to affect balance. To determine general cognitive function, physical activity in daily life, and lower extremity function, each subject completed the mini mental state examination (MMSE), the short questionnaire to assess health-enhancing physical activity (SQUASH), and the short physical performance battery (SPPB) (Table 1). Prior to their participation, subjects signed an informed consent document. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

Table 1 | Subject characteristics.

	Young adults	Old adults
Age (years)	23.2 ± 2.7	65.8 ± 4.5
Sex (male; female)	10; 10	9; 10
BMI (kg/m^2)	22.1 ± 2.5	26.0 ± 3.1
SPPB score	12.0 ± 0.0	11.8 ± 0.5
MMSE score	29.9 ± 0.5	28.8 ± 1.9
SQUASH		
- total score	11343 ± 5,156	10019 ± 3900
- light (min/w)	1823 ± 899	1337 ± 1,052
- moderate (min/w)	526 ± 373	503 ± 378
- heavy (min/w)	349 ± 312	564 ± 443

Values are mean ± SD, unless denoted differently. BMI: body mass index, SPBB: short physical performance battery (max. score of 12), MMSE: mini mental state examination (max. score of 30), SQUASH: short questionnaire to assess health-enhancing physical activity. Total score is minutes per week x intensity of the activity. The amount of light, moderate and heavy exercise is expressed in minutes per week.

2.2. Experimental procedures

Subjects were instructed to stand upright on two force plates (Bertec 4060-08, Columbus, OH, USA), wearing comfortable shoes without high heels. With the arms placed parallel to the body, subjects looked at a "+" sign displayed on a projection screen. Markings on the force platform around the shoes ensured consistent foot positioning throughout the experiments (intermalleolar distance, young: 17 ± 0.9, old: 14 ± 0.9). The center of pressure (CoP) signal was sampled at 100 Hz and filtered using a fourth order low-pass Butterworth filter with a cut off frequency of 10 Hz.

TMS and PNS were applied separately during two standing conditions: unsupported and supported standing (Fig. 1). The order of condition and stimulation type was randomized between subjects. During unsupported standing, participants stood naturally upright. During supported standing, participants stood upright and were also asked to remain lightly in contact with a wooden board at the chest. The position of the board was adjusted for each participant so that their CoP position similar was between conditions.

2.3. EMG

Because of a technical malfunction, surface electromyography (EMG) of the right soleus muscle and tibialis anterior was recorded using two different systems from the same company (young adults: model Bagnoli-8, old adults: Trigno™ Wireless System, Delsys, Natick, MA, USA). Active electrodes (young adults: DE-2.1, old adults: Trigno wireless EMG sensor) were placed over the muscle belly and, in young adults, a reference electrode was placed on the medial aspect of the tibia. The EMG signal was amplified 1000x, sampled at 5 kHz (young adults) or 4 kHz (old adults), and bandpass filtered with a second order Butterworth filter (10 to 1000 Hz) using data acquisition interface and software (Power 1401 and Signal 5, Cambridge Electronics Design, Cambridge, UK). Subjects performed a maximum voluntary contraction (MVC) of the soleus and tibialis anterior. For the soleus, subjects were standing on the toes with resistance from a strap attached to a harness worn by the subjects. For the tibialis anterior, manual resistance was given by the experimenter while subjects were seated in a chair with the knee in 45° flexion and the ankle in neutral position. The MVC data were analysed with a 50-ms, root-mean-square, moving window algorithm. The background EMG in a 50-ms window before every TMS pulse was rectified, averaged, and expressed as a percentage of MVC.

2.4. Behavioral data acquisition and analysis

A two-second window before every TMS pulse was used for CoP data analysis. CoP position and velocity in the anteroposterior direction was calculated for each of these time periods and then averaged across time periods. CoP velocity is a reliable [10] and discriminative index of body sway [11].

2.5. PNS data acquisition and analysis

The tibial nerve of the right leg was stimulated in the popliteal fossa using a constant-current stimulator (Digitimer DS 7, Hertfordshire, UK). The stimulating electrode (bipolar, cathode proximal) was fixed tightly with a Velcro strap around the leg. A recruitment curve was assembled by increasing stimulation intensity in steps of 0.5 mA until the M-wave amplitude in the soleus no longer increased. When the M wave ceased to increase and plateaued, stimulation intensity was further markedly increased in order to ensure that the maximal M-wave was obtained. Stimulation intensity during the experiment was set at the intensity that evoked a response of 50% of the maximal H-reflex amplitude, on the ascending part of the recruitment curve. Using this stimulation intensity, 20 H-reflexes were evoked during supported and unsupported standing. To reduce variability in the H-reflex [1], PNS was triggered only when CoP moved forward, as assessed online using CoP velocity, and with a minimal interval of five seconds between trials. H-reflex and M-wave amplitude were expressed as a percentage of the M-max.

2.6. TMS data acquisition and analysis

Transcranial magnetic stimuli were delivered to the cranium over the left M1 with a double cone coil (inner loop diameter 110 mm) connected to a Magstim 200[2] and Bistim[2] (Magstim, Whitland, UK). The current flowed from the anterior to posterior direction in the coil. The optimal location for eliciting motor evoked potentials (MEPs) with the largest amplitude at a given intensity in the soleus of the right leg was determined by moving the coil systematically in steps of 0.5 cm over M1 area starting at the vertex. The final location was marked on the scalp with a permanent marker to enable the experimenter to hold the coil at a consistent stimulation location throughout the experiment. We determined the motor threshold (MT) in the supported standing condition. MT was the lowest intensity at which the MEPs in the soleus were larger than 100 μV in at least three out of five consecutive trials [1,12,13]. Stimulation intensity of the conditioning and test pulse was set at 0.8 and 1.2 MT, respectively. As recommended by Garry & Thomson [14], we did not adjust the stimulation intensity between conditions, as SICI is influenced by stimulation intensity rather than test MEP size [14,15]. Paired-pulse TMS with an interstimulus interval of 2.5 ms was used to assess SICI, while an interstimulus interval of 13 ms was used to assess ICF. In preliminary studies we found these intervals to produce, the largest SICI and ICF, respectively, consistent with the literature [3]. In both conditions, there were 10 test MEP, 10 SICI, and 10 ICF trials, presented in a randomized order. Stimuli were only given in the forward phase of sway and with a minimal interval of five seconds between trials.

MEP size was quantified by calculating the peak-to-peak amplitude. SICI and ICF were expressed as percentage inhibition and facilitation, by using the following formula for SICI: 100 - (conditioned MEP/test MEP x 100), and the following formula for ICF: (conditioned MEP/test

MEP x 100) - 100. Although stimulation location and intensity were set for the soleus, in 15 young and 11 old subjects we managed to concurrently record consistent MEPs in the tibialis anterior. Therefore, data from the tibialis anterior is also presented.

2.7. Statistical analysis

All variables were checked for Gaussian distribution prior to analysis. An independent sample t-test was used to check differences in MT between young and old adults. CoP position, CoP velocity, background EMG, H-reflex amplitude, M-wave amplitude, test MEP amplitude, SICI, ICF were analyzed using an Age (young, old) by Condition (supported standing, unsupported standing) ANOVA with repeated measure on Condition. A series of covariance analysis were conducted to test whether significant Condition effects were confounded by differences between conditions in background EMG, test MEP amplitude and CoP position. Significant Age effects were tested for possible confounders using Pearson correlation. The alpha level was set at 0.05. Data are presented as mean ± SD.

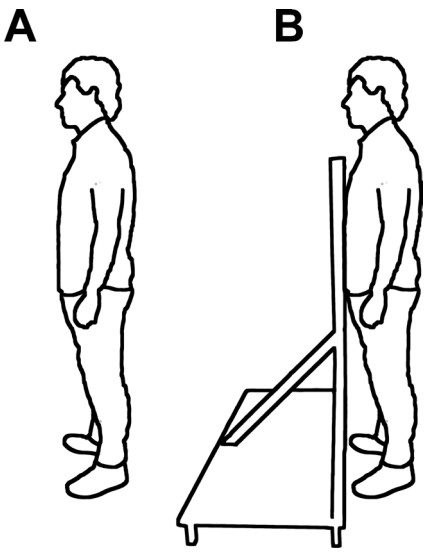


Figure 1 | Illustration of (**A**) unsupported and (**B**) supported standing conditions.

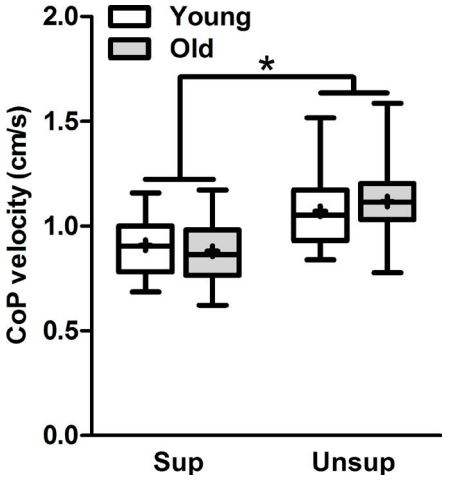


Figure 2 | Group data for young and old adults' center of pressure velocity in the anteroposterior direction when standing supported (sup) and unsupported (unsup), showing a significant Condition effect ($p < 0.001$). The horizontal line within the box indicates the median value, the box covers the 25th–75th percentiles, and the whiskers represent the range.

3. RESULTS

3.1. Center of Pressure

Mean CoP position was 1.5 ± 0.3 cm more forward ($F_{1,25}$ = 29.2, p < 0.001) and CoP velocity was 23 ± 12% greater ($F_{1,25}$ = 21.1, p < 0.001) during unsupported compared with supported standing (Fig. 2). There were no Age (position: $F_{1,25}$ = 1.5, p = 0.229; velocity: $F_{1,25}$ = 0.4, p = 0.397) or Age by Condition interaction effects (position: $F_{1,25}$ = 0.1, p = 0.727; velocity: $F_{1,25}$ = 0.5 ,p = 0.492).

3.2. Background EMG

There was a significant Condition effect ($F_{1,26}$ = 32.4, p < 0.001) in background EMG in the soleus muscle (Fig. 3A), with ~40% higher muscle activity in unsupported vs. supported standing. There was, however, no Age effect ($F_{1,26}$ = 0.9, p = 0.355) or Age by Condition interaction ($F_{1,26}$ = 2.2, p = 0.153). For the tibialis anterior background EMG, there were no Age and Condition effects, although there was a trend for greater background EMG in old vs. young adults ($F_{1,24}$ = 4.0, p = 0.057) and during supported vs. unsupported standing ($F_{1,24}$ = 4.2, p = 0.052) (Fig. 3B). There was an Age by Condition interaction ($F_{1,24}$ = 5.0, p = 0.035), with the background EMG being almost twice as high in supported vs. unsupported standing in old but not in young adults. Note that the overall background EMG level in the tibialis anterior was only 0.8% and 2.0% of MVC in young and old adults, respectively, suggesting that it had minimal, if any, effects on SICI and ICF.

3.3. PNS measures

There were no significant differences in the H-reflex amplitude between age groups (Young: 17 ± 1% of M-max; Old: 16 ± 2%) or support conditions (Supported: 16 ± 1%; Unsupported: 17 ± 2%) ($F_{1,31}$ < 0.1 ,p = 0.807; $F_{1,31}$ = 2.8 ,p = 0.105). In 10 young and 13 old subjects the H-reflex was accompanied by an M-wave. M-wave amplitudes were similar in the two age groups (Young: 8 ± 2%; Old: 15 ± 3%; $F_{1,21}$ = 1.7 ,p = 0.212) and two standing conditions (Supported: 13 ± 3%; Unsupported 11 ± 3%; $F_{1,21}$ = 0.6 ,p = 0.465).

3.4. TMS measures in the soleus

MT was similar in young (48 ± 5% of maximal stimulator output, range 40-55%) and old (51 ± 6%, range 38-60%) adults (t_{26} = -1.7, p = 0.101), resulting in similar stimulation intensities (1.2*MT). Old vs. young adults tended to have greater test MEP amplitude recorded in the soleus (old: 0.34 ± 0.19 mV; young: 0.23 ± 0.12 mV; $F_{1,26}$ = 3.8, p = 0.063). The test MEP increased from supported (0.27 ± 0.17 mV) to unsupported (0.31 ± 0.16 mV) standing ($F_{1,26}$ = 5.9, p = 0.022).

Fig. 4 illustrates the effect of standing support on TMS responses in the soleus muscle of a representative young and old subject. Across all subjects, Age did not affect SICI ($F_{1,26}$ = 0.3, p = 0.591) but SICI was 30% lower in unsupported compared with supported standing ($F_{1.26}$ = 8.6,

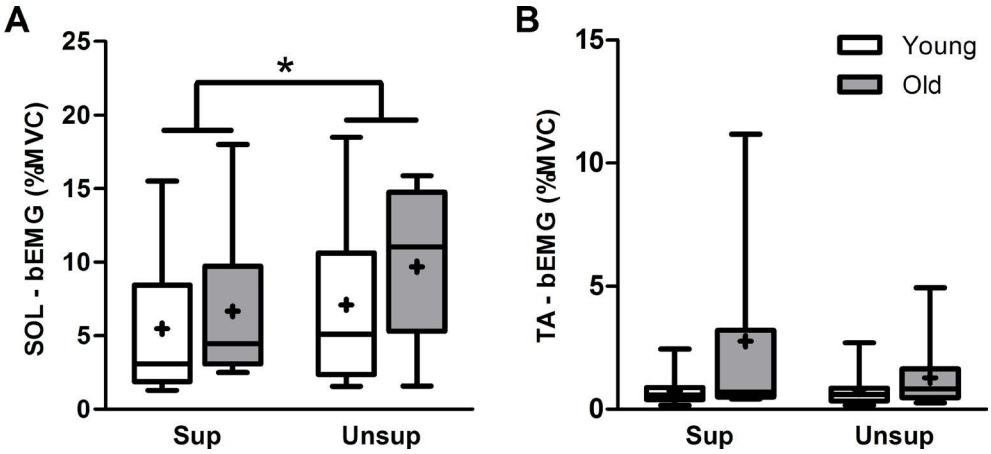


Figure 3 | Group data for young and old adults of background EMG in (**A**) the soleus muscle (Condition effect, $p < 0.001$), and (**B**) the tibialis anterior muscle (Interaction effect, $p = 0.035$). MVC: maximum voluntary contraction. The horizontal line within the box indicates the median value, the box covers the 25th–75th percentiles, and the whiskers represent the range.

Figure 4 | Representative responses to transcranial magnetic brain stimulation in the soleus muscle of one 23-year-old male and one 62-year-old male subject while standing supported (sup) and unsupported (unsup). Waveforms represent the average of 10 motor evoked potentials in response to an unconditioned test pulse (thin gray line) and to a conditioned test pulse (thick black line) given at an inter-pulse interval of 2.5 ms. Black arrows indicate the time when the test pulse is given. Note the down-modulation of short interval intracortical inhibition (SICI) when standing unsupported vs. supported in both young and old subjects.

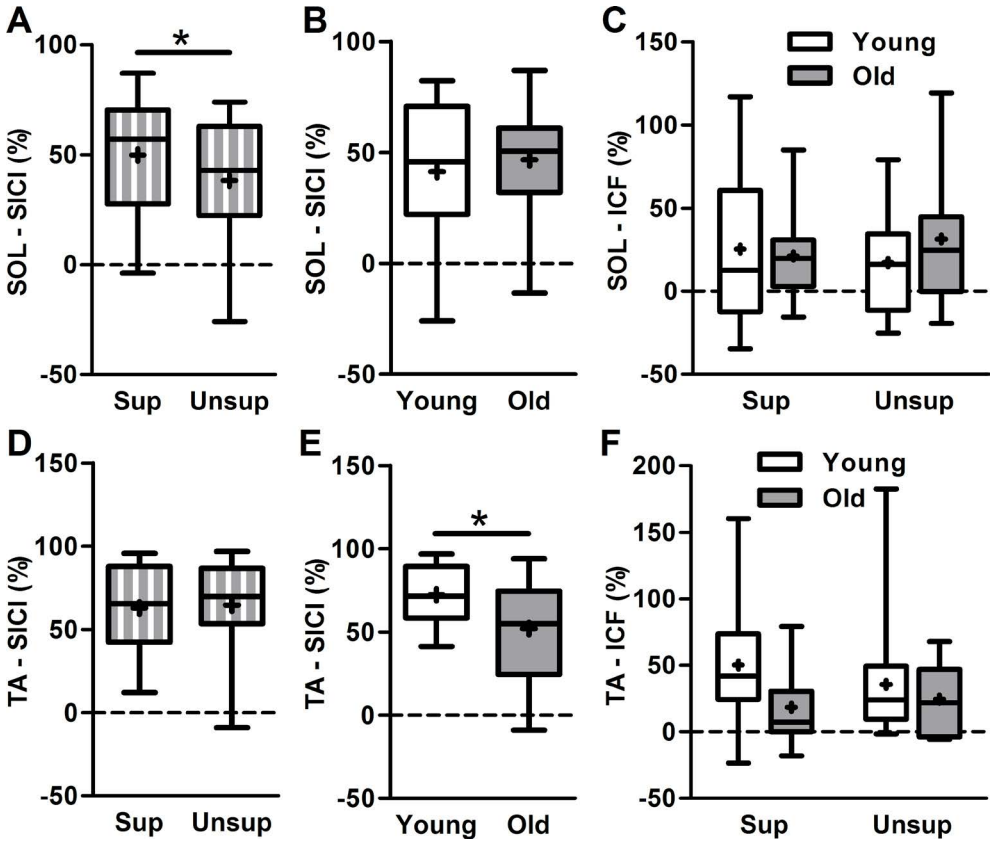


Figure 5 | Group data for (**A**) short interval intracortical inhibition (SICI) in the soleus during supported and unsupported standing (Condition effect, p = 0.007), (**B**) SICI in the soleus in young and old adults (no Age effect), (**C**) intracortical facilitation (ICF) in the soleus, (**D**) SICI in the tibialis anterior during supported and unsupported standing (no Condition effect), (E) SICI in the tibialis anterior in young and old adults (Age effect, p = 0.030), and (**F**) ICF in the tibialis anterior muscle. Greater values for SICI and ICF represent more inhibition and facilitation, respectively. Sup: supported, unsup: unsupported. The horizontal line within the box indicates the median value, the box covers the 25th–75th percentiles, and the whiskers represent the range.

p = 0.007) (Fig. 5a-b). Age and Condition had no effect on ICF ($F_{1,25}$ = 0.2, p = 0.679; $F_{1,25}$ = 0.02, p = 0.885) (Fig. 5c). There were no Age by Condition interaction in any of the TMS measures (test MEP: $F_{1,26}$ = 0.4, p = 0.532; SICI: $F_{1,26}$ =0.3, p = 0.574; ICF: $F_{1,25}$ = 1.3, p = 0.258).

To determine if potential confounders affected our main results, we conducted a series of covariance analyses. When the difference in background EMG between the two standing conditions was added as a covariate in the analysis, the Condition effect on test MEP amplitude was no longer significant ($F_{1,25}$ < 0.1, p = 0.879). However, the Condition effect on SICI remained significant when adding differences between conditions in background EMG ($F_{1,25}$ = 5.1, p = 0.033), test MEP size ($F_{1,25}$ = 8.6, p = 0.007), and CoP position ($F_{1,24}$ = 4.5, p = 0.045), respectively.

3.5. TMS measures in the tibialis anterior

In the tibialis anterior, test MEP size was greater in old (0.72 ± 0.33 mV) compared with young (0.36 ± 0.29 mV) adults ($F_{1,24}$ = 9.7, p = 0.005) but was similar in supported (0.52 ± 0.38 mV) and unsupported (0.50 ± 0.34 mV) standing ($F_{1,24}$ = 0.6, p = 0.441). In contrast to the soleus, there was ~30% less SICI in old vs. young adults ($F_{1,24}$ = 5.3, p = 0.030) (Fig. 5D-E) but SICI was similar between standing conditions ($F_{1,24}$ = 0.3, p = 0.597). Age and Condition did not affect ICF in the tibialis anterior (Age: $F_{1,23}$ = 2.2, p = 0.155; Condition: $F_{1,23}$ = 0.5, p = 0.510) (Fig. 5F). There were no Age by Condition interaction in any of the TMS measures (test MEP: $F_{1,24}$ = 1.9, p = 0.181; SICI: $F_{1,24}$ = 0.1, p = 0.822; ICF: $F_{1,23}$ = 3.0, p = 0.099). There was no correlation between test MEP size and SICI (Young: r = 0.07, p = 0.701; Old: r = -0.18, p = 0.418), showing that the Age effect in SICI was not due to the Age effect in test MEP size.

4. DISCUSSION

Recently, we have shown an age-related reduction in SICI with an increase in balance task demand [9]. The present study extends these previous findings by determining whether the age-related difference in modulation of intracortical circuits is also present when switching from a non-balance task (i.e., supported standing) to a relatively simple balance task i.e., normal standing on rigid surface. The present results revealed a task-related modulation of SICI independent of age, highlighting the importance of task difficulty on age-related differences in SICI. An additional new finding is that the age-effects on SICI are muscle-specific, as age affected SICI in the tibialis anterior but not in the soleus muscle. Neither age nor standing condition affected the H-reflex amplitude in the soleus.

4.1. Posture-related modulation of SICI in young and old adults

SICI in the soleus was lower in both age groups in the unsupported compared with supported condition. Reductions in SICI in relation to motor tasks have been reported previously, for example, during movement preparation [16] and during the activation phase compared with the deactivation phase in cycling [17]. In a previous study we found a down-modulation of SICI in old but not in young adults when standing on foam vs. standing on a rigid surface [9]. We argued that the change from rigid to foam surface challenged old compared with young subjects more, reflected by the 47% and 20% increase in sway velocity in old and young subjects, respectively [9]. In the current study, changes in sway velocity were comparable between young and old participants when switching from supported to unsupported standing. Thus, it seems that elderly subjects have similar strategies to adapt SICI when considering simple, non-challenging balance tasks. In contrast, when postural demands are high, the threshold for disinhibition seems to be lower [9]. Possibly, a decrease in SICI heightens the state of readiness in M1 and prepares it to become

more easily activated or to activate other neural structures on demand. This interpretation fits well with the current data concerning a switch from a non-balance to a simple balance task: a reduction in SICI would set M1 and perhaps related motor structures in a state that would allow more effective responses to potential balance threats. An alternative interpretation is that SICI is reduced in order to activate the muscles around the ankle and ensure ankle stiffness. However, this seems unlikely, as the modulation of SICI was not related to changes in background EMG, a finding discussed below.

We considered the impact of potential confounders on our main finding, i.e., postural modulation of SICI. Covariance analyses showed that test MEP size, CoP position and background EMG did not affect the SICI modulation between standing conditions. The Condition effect on test MEP size, however, was mediated by the increased level of background EMG. These results are supported by a sub-analysis of the subjects who had only minor changes in background EMG between conditions (0.3 ± 1.4% of MVC increase from supported to unsupported standing). In this sub-group of eight subjects (5 young, 3 old), half increased and half decreased their test MEP amplitude from supported to unsupported standing. On the contrary, seven out of the eight subjects decreased their SICI. Also, the average decrease in SICI is similar in this subgroup (29%) compared to the rest of the subjects (30%). Our protocol of not adjusting test MEP size between conditions is strongly supported by previous data showing that SICI should be examined using constant test TMS intensity regardless of changes in test MEP size. Therefore, the modulation in SICI was related to the switch from a non-balance task to a balance task and not to differences in background EMG or MEP size.

Interestingly, the SICI modulation was muscle specific, as young and old adults did not show any modulation in SICI when measured in the tibialis anterior but did show modulation with standing conditions when measured in the soleus muscle. This observation is consistent with data from Soto and colleagues [3], showing a reduction in SICI in the soleus but not in the tibialis anterior when standing compared to rest, and agrees with the role of the plantar flexors as being the agonistic muscles for standing [18].

4.2. Age-related changes in SICI are muscle-specific

In the present study, there were no age-related changes in SICI in the soleus muscle. In our previous study we found lower SICI in old compared with young adults in the tibialis anterior [9]. These results might signify that age-related changes are muscle-specific. Indeed, the data that we obtained from the tibialis anterior in the current study were consistent with the data from our previous study, showing an age-related reduction in SICI. This muscle-specificity may be related to different neural circuits controlling the soleus and tibialis anterior muscles. An functional magnetic resonance imaging study in healthy young adults reported that dorsal flexion evoked extensive brain activation in motor cortical areas, whereas plantar flexion mainly activated sub-

cortical structures [19]. Moreover, motor unit recordings after single TMS pulses showed that corticospinal projections to the soleus muscle were weaker compared to those to the tibialis anterior [20]. Additional evidence supporting the hypothesis of a specific age-related reduction in SICI for muscles with strong corticospinal projections comes from muscles of the upper extremity. When examined in hand muscles, reduced [16,21] or similar [22,23] SICI has been reported in old compared with young adults. However, when examined in wrist flexors and extensors, which have weaker monosynaptic projections, SICI was greater in middle-aged and old adults [24,25]. The present study is the first to demonstrate this age by muscle interaction within a study and in relation to upright standing.

4.3. No age- or posture-related changes in ICF

Consistent with our previous study, we found no age- or posture-related changes in ICF. This may indicate that modulating the descending drive to lower limb muscles during upright standing depends on up- or down-regulation of intracortical inhibition (disinhibition) and not facilitation. Reducing inhibition is possibly preferred over increasing facilitation to limit induced noise.

4.4. No age- or posture- related changes in H-reflex

In the present study, there were no age- or posture- related changes in H-reflex amplitude. This is inconsistent with Tokuno and colleagues [1], who reported reduced H-reflex amplitude during unsupported compared with supported standing. Furthermore, most previous studies reported reduced H-reflex with increased age and balance task difficulty [6,26,27]. As the methodology used in previous studies is comparable to ours, it is unclear what caused this inconsistency. One possible explanation is that we had a greater increase in background EMG between conditions compared to the other two studies. This increase in background EMG may have facilitated the H-reflex size and therefore counteracted the potential decrease due to balance task difficulty. A decreased H-reflex combined with an increased corticospinal or intracortical excitability would suggest an increased descending drive to control leg muscles during upright stance [6]. However, the current results can neither confirm nor disprove this hypothesis.

4.5. Clinical implication of the results

The current and previous data are compatible with the concept of prescribing exercise training that includes balance tasks with increasing difficulty for old adults. Task difficulty, perhaps a proxy for 'intensity' of balance training, may be an important element of these exercise programs and should possibly be relatively high and incremental in order to cause favorable neural adaptations [28]. Future studies will verify this suggestion because currently there are no studies that report changes in M1 intracortical circuits after balance training in old adults.

4.6. Limitations of the study

We recorded responses in one muscle (tibialis anterior) to TMS while actually targeting another muscle (soleus), a method used previously [3,29]. Although this method has its limitations, generally the threshold of the tibialis anterior is lower compared with the soleus so that many subjects produce reliable responses in the tibialis anterior to suprathreshold TMS targeting the soleus and these responses are not the result of cross-talk but instead are muscle-specific responses to the stimulation [30,31]. Moreover, the degree of inhibition and the age-related differences in the present study (Young: 73 ± 5%, Old: 53 ±9%) were comparable to our previous study (Young: 67 ± 8%, Old: 44 ± 5%) where we did target the tibialis anterior [9], suggesting that the tibialis anterior data in the present study are in all likelihood reliable. Another limitation is that most participants were relatively fit and physically active, shown by the high SPPB and SQUASH scores. Therefore, the results are relevant to a fit segment of seniors and may not be generalizable to less active individuals, in whom an age-effect could be more prominent.

4.7. Conclusions

The present study demonstrates that intracortical inhibition in the soleus muscle decreased when subjects changed from a non-balance to a balance task in which the nervous system needs to control body sway. In contrast to the results of our previous study that involved much more challenging balance tasks and therefore highlighting the importance of task difficulty, the modulation of SICI was independent of age. Moreover, the present results strengthen the hypothesis of a specific age-related reduction in SICI preferentially for muscles with strong corticospinal projections. Overall, a combination of past and current data suggests that the M1 is involved in standing control and that its role becomes more prominent with an increase in task difficulty and age.

REFERENCES

1. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of human standing. Acta Physiol (Oxf) 2009 Mar;195(3):385-395.

2. Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, et al. Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. Clin Neurophysiol 2000 May;111(5):794-799.

3. Soto O, Valls-Sole J, Shanahan P, Rothwell J. Reduction of intracortical inhibition in soleus muscle during postural activity. J Neurophysiol 2006 Oct;96(4):1711-1717.

4. Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A. Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. J Appl Physiol 2006 Aug;101(2):420-429.

5. Baudry S, Penzer F, Duchateau J. Vision and proprioception do not influence the excitability of the corticomotoneuronal pathway during upright standing in young and elderly adults. Neuroscience 2014 May 30;268:247-254.

6. Baudry S, Penzer F, Duchateau J. Input-output characteristics of soleus homonymous Ia afferents and corti-

cospinal pathways during upright standing differ between young and elderly adults. Acta Physiol (Oxf) 2014 Mar;210(3):667-677.

7. Koceja DM, Mynark RG. Comparison of heteronymous monosynaptic Ia facilitation in young and elderly subjects in supine and standing positions. Int J Neurosci 2000 Jul-Aug;103(1-4):1-17.

8. Baudry S, Duchateau J. Age-related influence of vision and proprioception on Ia presynaptic inhibition in soleus muscle during upright stance. J Physiol 2012 Nov 1;590(Pt 21):5541-5554.

9. Papegaaij S, Taube W, Hogenhout M, Baudry S, Hortobagyi T. Age-related decrease in motor cortical inhibition during standing under different sensory conditions. Front Aging Neurosci 2014 Jun 12;6:126.

10. Demura S, Kitabayashi T, Aoki H. Body-sway characteristics during a static upright posture in the elderly. Geriatr Gerontol Int 2008 Sep;8(3):188-197.

11. Raymakers JA, Samson MM, Verhaar HJ. The assessment of body sway and the choice of the stability parameter(s). Gait Posture 2005 Jan;21(1):48-58.

12. Taube W, Lundbye-Jensen J, Schubert M, Gollhofer A, Leukel C. Evidence that the cortical motor command for the initiation of dynamic plantarflexion consists of excitation followed by inhibition. PLoS One 2011;6(10):e25657.

13. Beck S, Taube W, Gruber M, Amtage F, Gollhofer A, Schubert M. Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. Brain Res 2007 Nov 7;1179:51-60.

14. Garry MI, Thomson RH. The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. Exp Brain Res 2009 Feb;193(2):267-274.

15. Zoghi M, Nordstrom MA. Progressive suppression of intracortical inhibition during graded isometric contraction of a hand muscle is not influenced by hand preference. Exp Brain Res 2007 Feb;177(2):266-274.

16. Heise KF, Zimerman M, Hoppe J, Gerloff C, Wegscheider K, Hummel FC. The Aging Motor System as a Model for Plastic Changes of GABA-Mediated Intracortical Inhibition and Their Behavioral Relevance. J Neurosci 2013 May 22;33(21):9039-9049.

17. Sidhu SK, Cresswell AG, Carroll TJ. Short-interval intracortical inhibition in knee extensors during locomotor cycling. Acta Physiol (Oxf) 2013 Jan;207(1):194-201.

18. Di Giulio I, Maganaris CN, Baltzopoulos V, Loram ID. The proprioceptive and agonist roles of gastrocnemius, soleus and tibialis anterior muscles in maintaining human upright posture. J Physiol 2009 May 15;587(Pt 10):2399-2416.

19. Trinastic JP, Kautz SA, McGregor K, Gregory C, Bowden M, Benjamin MB, et al. An fMRI study of the differences in brain activity during active ankle dorsiflexion and plantarflexion. Brain Imaging Behav 2010 Jun;4(2):121-131.

20. Brouwer B, Ashby P. Corticospinal projections to lower limb motoneurons in man. Exp Brain Res 1992;89(3):649-654.

21. Marneweck M, Loftus A, Hammond G. Short-interval intracortical inhibition and manual dexterity in healthy aging. Neurosci Res 2011 Aug;70(4):408-414.

22. Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, et al. Effects of aging on motor cortex excitability. Neurosci Res 2006 May;55(1):74-77.

23. Smith AE, Ridding MC, Higgins RD, Wittert GA, Pitcher JB. Cutaneous afferent input does not modulate

motor intracortical inhibition in ageing men. Eur J Neurosci 2011 Nov;34(9):1461-1469.

24. Kossev AR, Schrader C, Dauper J, Dengler R, Rollnik JD. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. Neurosci Lett 2002 Nov 22;333(2):83-86.

25. McGinley M, Hoffman RL, Russ DW, Thomas JS, Clark BC. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. Exp Gerontol 2010 Sep;45(9):671-678.

26. Koceja DM, Markus CA, Trimble MH. Postural modulation of the soleus H reflex in young and old subjects. Electroencephalogr Clin Neurophysiol 1995 Dec;97(6):387-393.

27. Angulo-Kinzler RM, Mynark RG, Koceja DM. Soleus H-reflex gain in elderly and young adults: modulation due to body position. J Gerontol A Biol Sci Med Sci 1998 Mar;53(2):M120-5.

28. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc 2008 Dec;56(12):2234-2243.

29. Yamaguchi T, Fujiwara T, Liu W, Liu M. Effects of pedaling exercise on the intracortical inhibition of cortical leg area. Exp Brain Res 2012 May;218(3):401-406.

30. Geertsen SS, Zuur AT, Nielsen JB. Voluntary activation of ankle muscles is accompanied by subcortical facilitation of their antagonists. J Physiol 2010 Jul 1;588(Pt 13):2391-2402.

31. Hansen NL, Conway BA, Halliday DM, Hansen S, Pyndt HS, Biering-Sorensen F, et al. Reduction of common synaptic drive to ankle dorsiflexor motoneurons during walking in patients with spinal cord lesion. J Neurophysiol 2005 Aug;94(2):934-942.

CHAPTER 5

Postural challenge affects motor cortical activity in young and old adults

S. Papegaaij

W. Taube

H.G. van Keeken

E. Otten

S. Baudry

T. Hortobágyi

Experimental Gerontology 2015 November: In press.

ABSTRACT

When humans voluntarily activate a muscle, intracortical inhibition decreases. Such a decrease also occurs in the presence of a postural challenge and more so with increasing age. Here, we examined age-related changes in motor cortical activity during postural and non-postural contractions with varying levels of postural challenge. Fourteen young (age 22) and twelve old adults (age 70) performed three conditions: (1) voluntary contraction of the soleus muscle in sitting and (2) leaning forward while standing with and (3) without being supported. Subthreshold transcranial magnetic stimulation was applied to the soleus motor area suppressing ongoing EMG, as an index of motor cortical activity. The area of EMG suppression was ~60% smaller ($p<0.05$) in unsupported vs. supported leaning and sitting, with no difference between these latter two conditions ($p>0.05$). Even though in absolute terms young compared with old adults leaned farther ($p=0.018$), there was no age effect or an age by condition interaction in EMG suppression. Leaning closer to the maximum without support correlated with less EMG suppression (rho=-0.44, $p=0.034$). We conclude that the critical factor in modulating motor cortical activity was postural challenge and not contraction aim or posture. Age did not affect the motor control strategy as quantified by the modulation of motor cortical activity, but the modulation appeared at a lower task difficulty with increasing age.

1. INTRODUCTION

Although historical studies in intact and decerebrate animals identified subcortical neural circuits, especially spinal reflexes, as centers to control upright standing [1,2], recent studies have provided evidence for the involvement of the motor cortex [3-6]. However, it remains elusive if the motor cortical control differs between voluntary and postural contractions and if age affects this control [7].

When humans voluntarily activate a muscle, the magnitude of short-interval intracortical inhibition (SICI) decreases [8-11]. It is thought that inhibitory intracortical circuits modulate the excitability of the cortical neurons that project to the spinal motor neurons of the muscles involved in the task [12]. The degree of reduction in intracortical inhibition is related to contraction intensity [9,11], contraction type [13], and whether the movement starts or ends [14]. SICI is also modulated during postural contractions, defined as contractions with the aim to maintain a certain posture, as shown by a reduction in SICI in the soleus muscle during standing as compared with sitting [15].

In addition to the aim of the contraction (postural vs. non-postural), postural challenge may also affect inhibition. We define postural challenge as the degree of difficulty one encounters in holding a specific body position. SICI in the tibialis anterior is lower during standing as compared with sitting, even though this muscle is only weakly activated during these tasks [16]. Such a context-related reduction in SICI suggests that increased postural challenge is coupled with higher motor cortical excitability. A limitation of comparing sitting with standing is that not only postural challenge but also posture itself is different between conditions, which may affect motor cortical excitability [17,18]. However, also when normal standing was compared with supported standing, motor cortical excitability in the soleus muscle was higher [3] and SICI was lower [19] during normal standing. The emerging picture is that the motor cortex is involved in postural contractions to control upright standing and that its excitability increases with increasing postural challenge.

There is some evidence that the postural challenge-related increase in motor cortical excitability increases with age. When healthy adults stood on a rigid surface and then on foam, this increase in postural challenge resulted in a decrease in SICI in old but not in young adults' tibialis anterior muscle [20]. However, this age by condition interaction was not present in normal standing, a relatively easy postural task [19,21]. Therefore, it is unclear if the modulation between a stable and unstable condition in old adults reflects a different motor control strategy or different relative task difficulty (i.e., the same task being more difficult for old than young adults). Moreover, it is unclear if age affects the motor cortical control of postural and non-postural contractions.

Therefore, the aim of the current study was to examine age-related changes in motor corti-

cal activity during non-postural and postural contractions in a postural challenging and non-challenging context. Subjects were asked to (1) voluntarily contract the soleus muscle during sitting (SIT), (2) lean forward during standing, with support at the chest (SL), and (3) lean forward during standing, without support (UL). These conditions allowed us to disentangle the effects of contraction aim, postural challenge, and posture, and to investigate the interaction with age. To examine motor cortical activity, we applied transcranial magnetic stimulation pulses at subthreshold intensities (subTMS). Such pulses suppress ongoing electromyographic (EMG) activity through the activation of inhibitory intracortical circuits [22].

Based on fMRI and TMS studies, suggesting that motor control relies more on cortical structures in old compared with young adults [20,23-25], we hypothesized an age by condition interaction in motor cortical activity as indexed by TMS-induced EMG suppression. We also expected that the pattern of changes in EMG suppression between the conditions would provide insights into which of the three factors (contraction aim, postural challenge, posture) is critical in modulating motor cortical activity (see Fig. 1). If contraction aim is a critical factor, we would expect a gradual change in TMS-induced EMG suppression from sitting to supported leaning to unsupported leaning. We note that during supported leaning the contraction was a combined postural and non-postural contraction. As support was provided only at the chest, a postural contraction was still needed to prevent the body from buckling at the hip. To reach the target EMG level subjects were instructed to add a small amount of voluntary activation to the ongoing activation produced by the postural contraction, resulting in a mix of voluntary and postural soleus activation. If postural challenge is a critical factor in modulating motor cortical activity, we would expect similar TMS-induced EMG suppression in sitting and supported leaning, with different suppression in unsupported leaning. If posture is critical, we would expect supported and unsupported leaning to be similar, with different TMS-induced EMG suppression in sitting.

2. MATERIALS AND METHODS

2.1. Subjects

Sixteen young (20-31 years) and seventeen old adults (64-83 years) participated in the study (Table 1). Participants were free of neurological or orthopedic conditions, non-dental associated metal within the cranium, did not take neuroactive drugs or drugs known to affect balance, and reported to be not pregnant. General cognitive function was assessed by the Mini-Mental State Examination (MMSE) and physical activity level by the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH). Lower extremity function was evaluated by the Short Physical Performance Battery (SPPB), including standing balance, walking speed and chair stand tests [26]. Before the experiment, all subjects signed an informed consent document approved by the Medical Ethics Committee of the University Medical Center Groningen.

Table 1 | Subject characteristics.

	Young adults	**Old adults**
Age (years)*	22.1 ± 0.9	71.3 ± 1.1
Sex (male; female)	8; 8	7; 10
Height (m)*	1.78 ± 0.02	1.72 ± 0.02
BMI (kg/m^2)*	22.3 ± 0.4	25.3 ± 0.8
SPPB score*	12.0 ± 0.0	11.5 ± 0.2
MMSE score*	29.8 ± 0.1	28.4 ± 0.3
SQUASH:		
- total score	8904 ± 798	7636 ± 630
- light (min/w)*	1859 ± 180	851 ± 135
- moderate (min/w)	321 ± 72	199 ± 41
- heavy (min/w)*	243 ± 44	516 ± 71

Values are mean ± SE, unless denoted differently. BMI: body mass index, SPBB: short physical performance battery (max. score of 12), MMSE: mini mental state examination (max. score of 30), SQUASH: short questionnaire to assess health-enhancing physical activity. Total score is minutes per week x intensity of the activity. The amount of light, moderate and heavy exercise is expressed in minutes per week. * denotes a significant difference between young and old adults ($p<0.05$).

2.2. Experimental protocol

The experiments were conducted in one, 3-hour-long session. Subjects were standing on two force platforms with the feet in a self-selected position that was marked on the force platforms to ensure consistent positioning throughout the experiment (intermalleolar distance, young: 17.3±1.1 cm, old: 14.0±1.1 cm). SubTMS was applied while subjects subsequently performed the following three tasks in a randomized order: unsupported leaning (UL), supported leaning (SL), and sitting (SIT). During UL, subjects were instructed to lean forward by dorsal flexing their ankles while keeping the rest of the body straight. Subjects received online feedback by watching a red ball moving over a black background, representing the movements of the CoP in the anterior-posterior direction. Upward movement of the ball corresponded to a forward shift of the CoP. A dark green horizontal line was set as a CoP target at 75% of the maximum voluntary and unaided forward lean. Thus, task difficulty was adjusted to individual skill level. Two light green horizontal lines at 70% and 80% of the maximum cued the subjects to keep the CoP on the dark green target line and within the 5% band around it. Subjects were instructed to try to keep the ball on the target line. During SL, the body position was kept the same as during UL but the subjects were supported at chest level by a sturdy and adjustable custom-made frame. Subjects were instructed to rest against the frame with full body weight. During SL and SIT, subjects matched the soleus

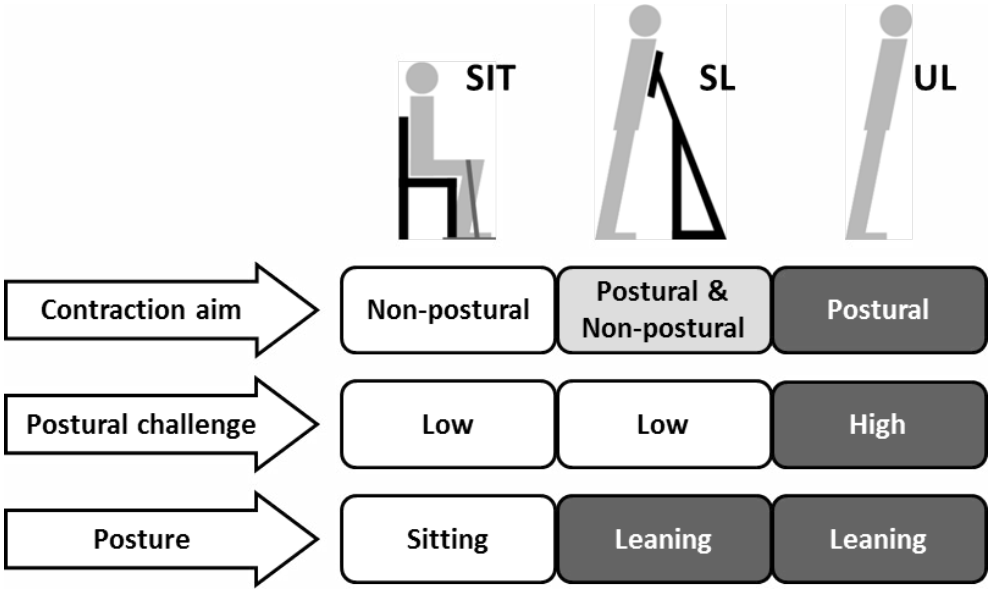


Figure 1 | A summary of experimental conditions and conceptual interactions between three different conditions (sitting - SIT, supported leaning - SL, unsupported leaning - UL) that could influence intracortical inhibition (contraction aim, postural challenge, posture).

EMG activity with that recorded during UL. In these conditions, instead of the red ball, subjects received online feedback in the form of the rectified and smoothed EMG signal displayed together with a horizontal target line. Subjects were instructed to try to keep the line of the ongoing EMG on the target line. In SL, subjects matched the EMG recorded in UL by putting more pressure on the right forefoot without changing posture. In SIT, the EMG matching was accomplished by raising the heel against resistance from a strap fixed tightly around the forefoot and over the knee. After each condition, subjects were asked to fill in the Borg Rating of Perceived Exertion (RPE) scale (ranging from 6 to 20) [27]. At the beginning of the experiment subjects were instructed to stand quietly for 10 s. These data were used as a reference to quantify forward lean and determine differences in joint angles between standing and leaning. Before and after the experiment, subjects performed another 30 s of UL without stimulation to determine if the experimental protocol caused fatigue.

2.3. Data acquisition

Parallel-bar EMG sensors (TrignoTM Wireless System, Delsys, Natick, MA, USA) were placed on the muscle belly of the soleus muscle of the preferred leg. The preference leg was determined by testing which foot was used when kicking a football, pushing an object with the foot, and stamping on the ground [28]. To minimize impedance, the skin was shaved, abraded with fine-grain

sandpaper, and cleaned with alcohol. Surface EMG was pre-amplified 300x in the sensor and then further amplified by a factor of 3.03 in the base station, resulting in a total signal amplification of 909. Signals were sampled at 4 kHz and bandpass filtered with a second order Butterworth filter (10-1000 Hz) using data acquisition interface and software (Power 1401 and Spike 7, Cambridge Electronics Design, Cambridge, UK). While seated, subjects performed two maximal voluntary contractions (MVC) of the soleus, with resistance from the same strap used during the sitting condition. The maximal EMG during the MVC was identified using a root-mean-square (RMS) algorithm with a 50-ms moving window.

An 11-video-camera motion analysis system (Vicon, Oxford, UK) recorded spatial coordinates of reflective markers placed on the right acromion, greater trochanter, lateral femoral epicondyle, lateral malleolus and fifth metatarsophalangeal joint. Two force plates (Bertec 4060-08, Columbus, OH, USA) were used to measure CoP displacement. Kinematic and CoP data was sampled at 100 Hz and zero-phase filtered using a fourth order low-pass Butterworth filter with a cut off frequency of 10 Hz.

2.4. Transcranial magnetic stimulation

A double cone coil (inner loop diameter 110 mm) connected to a Magstim 200^2 and Bistim2 (Magstim, Whitland, UK) was used to magnetically stimulate the primary motor cortex contralateral to the preferred leg. The coil, held by the experimenter, was positioned so that the current in the coil flowed in an anterior-to-posterior direction. The hotspot for the soleus muscle was located by moving the coil in a systematic manner laterally and posteriorly from the vertex in steps of 0.5 cm. This hotspot was marked on the scalp to enable the experimenter to hold the coil in the same position throughout the experiment. Active motor threshold (aMT) was defined as the minimum intensity at which an MEP above bEMG could be evoked in three out of five consecutive trials and was determined during SIT with subjects matching the soleus EMG activity recorded during UL. The MEP's recorded during this procedure were used to determine MEP onset. Stimulation intensity was then decreased to 80% of aMT and single pulses were given every 1.5 s. Responses were rectified and averaged over 20-40 trials, depending on the stability of the signal. Even though stimulation intensity was subthreshold, when averaging over multiple trials a facilitation in the EMG signal can sometimes be observed. Stimulation intensity was adjusted to get the greatest amount of TMS-induced EMG suppression without preceding facilitation. Subjects then received 4-6 blocks of 20 pulses per condition using this stimulation intensity. Rest periods of 30 s were given between blocks and rest periods of 5 min between conditions. As in previous studies using subTMS [22,29,30], two young and five old adults were excluded because they did not exhibit suppression without a preceding facilitation in all conditions.

2.5. Data analysis

Custom made scripts (Mathworks Matlab R2009b) were used for data analysis. EMG traces before and after the TMS pulses were rectified and averaged across trials. BEMG was calculated by averaging the rectified EMG from the 300 ms time window before stimulation. For every participant the MEP onset was determined from the data with suprathreshold TMS pulses. The onset of suppression after subTMS was defined as the first time point where the averaged EMG response was below the level of bEMG for at least 5 ms in the 30 ms time window starting at the MEP onset. The end of suppression was defined as the first time point where the averaged EMG response was above bEMG for longer than 1 ms. In two young and two old subjects this algorithm did not find any EMG suppression during UL, although it did find EMG suppression during SIT and SL. In these cases we determined the onset and end of suppression manually by visual inspection. Exclusion of these subjects did not affect the main results. We quantified EMG suppression as a product of the mean amplitude of suppression in percent of bEMG and the duration of suppression in ms (i.e., Amp_{norm}*ms). In most subjects we also observed a facilitation in EMG after the suppression. Quantification of the magnitude of this facilitation was done similarly as for the suppression. Finally, to assess fatigue, median frequency (MDF) of the EMG signal during unsupported leaning at the beginning and the end of the experiment was calculated.

Leaning performance was quantified by variability (SD) in the anterior-posterior position of the CoP and error from the target (absolute difference between mean CoP position and the target). The percentage lean was calculated by expressing the average of CoP position during leaning as a percentage of the maximum lean. Lastly, leaning strategy was quantified by the difference in ankle, knee and hip joint angles between leaning and standing, derived from reflective marker position data.

2.6. Statistical analysis

All variables were checked for normal distribution prior to analysis. Male/female proportions were compared between young and old adults using the chi-square test. Other subject characteristics (age, height, BMI, SPPB score, MMSE score, SQUASH scores) and behavioral measures during unsupported leaning (CoP variability, CoP error, maximum lean, percentage lean, joint angles) were compared between young and old adults using independent t-tests. An Age (young, old) by Condition (sitting, supported leaning, unsupported leaning) mixed model ANOVA was used for the analysis of bEMG, EMG suppression and EMG facilitation. Results showing a significant condition effect were subjected to a post hoc Tukey's test. In case of violation of the assumption of sphericity, a Greenhouse–Geisser correction was applied. The same analysis was repeated for EMG suppression and facilitation with bEMG as a covariate. An Age (young, old) by Time (pre, post) mixed model ANOVA was used for the analysis of EMG MDF during leaning before and after the experiment. To calculate correlation between EMG suppression and behavior, EMG suppres-

sion during unsupported leaning was expressed as a percentage of EMG suppression during supported leaning. Because of non-normal distribution of this variable, correlations between EMG suppression and percentage lean, CoP variability, CoP error and bEMG were determined using the Spearman correlation coefficient.

3. RESULTS

3.1. Behavioral results

There was no difference in percentage of lean between young and old adults ($t(11.7)=0.1$, $p=0.931$), with young adults leaning to 74.4±0.2% and old adults to 74.4±0.8% of their maximum. The maximum lean relative to average CoP position during standing was farther in young (92±8 mm) than in old (66±6 mm) adults ($t(21)=2.6$, $p=0.018$), even after correction for height ($t(21)=2.3$, $p=0.033$). Also, leaning performance was worse in old compared with young adults, with greater CoP variability (Young: 3.0±0.3mm, Old: 4.2±0.3mm; $t(21)=-2.7$, $p=0.013$) and error from the target (Young: 0.6±0.1mm, Old: 1.5±0.2mm; $t(12.5)=-3.7$, $p=0.003$).

Despite instructions to lean from the ankle, leaning strategies were slightly different between the two groups. Old adults showed a greater difference in hip angle between upright standing and leaning than young adults ($t(14)=-2.5$, $p=0.023$) and a trend towards a smaller difference in the ankle angle ($t(19)=1.7$, $p=0.099$). Differences in knee angle between standing and leaning were similar between the groups ($t(19)=0.3$, $p=0.794$).

3.2. EMG activity

As intended, the level of EMG activity did not change between conditions ($F(1.3, 30.7)=0.03$, $p=0.907$), but was higher in old (21.2±2.2% of MVC) compared with young (11.6±1.3% of MVC) adults ($F(1,24)=15.1$, $p=0.001$). There was no group by condition interaction ($F(1.3, 30.7)=2.3$, $p=0.130$).

3.3. TMS measures

Active motor threshold and TMS stimulation intensity were higher in old (aMT: 53±3%, stimulation intensity: 37±2%) compared with young (aMT: 45±2%, stimulation intensity: 30±2%) adults ($t(24)=-2.2$, $p=0.036$; $t(24)=-2.5$, $p=0.02$).

Figures 2 and 3 show respectively single subject and group data of EMG suppression and facilitation. The onset latency of EMG suppression was 42.6±1.4 ms in young and 48.4±2.2 ms in old adults, with a difference of 5.7±0.8 ms in young and 7.4±1.7 ms in old adults between EMG suppression onset and MEP onset. There was a condition effect on the area of EMG suppression ($F(2,48)=23.3$, $p<0.001$). Tukey's post hoc tests revealed that the area of EMG suppression was ~60% smaller in UL compared with SL and SIT ($p<0.05$). EMG suppression was similar in SL and SIT ($p>0.05$). There were no group effects or condition by group interaction effects on EMG sup-

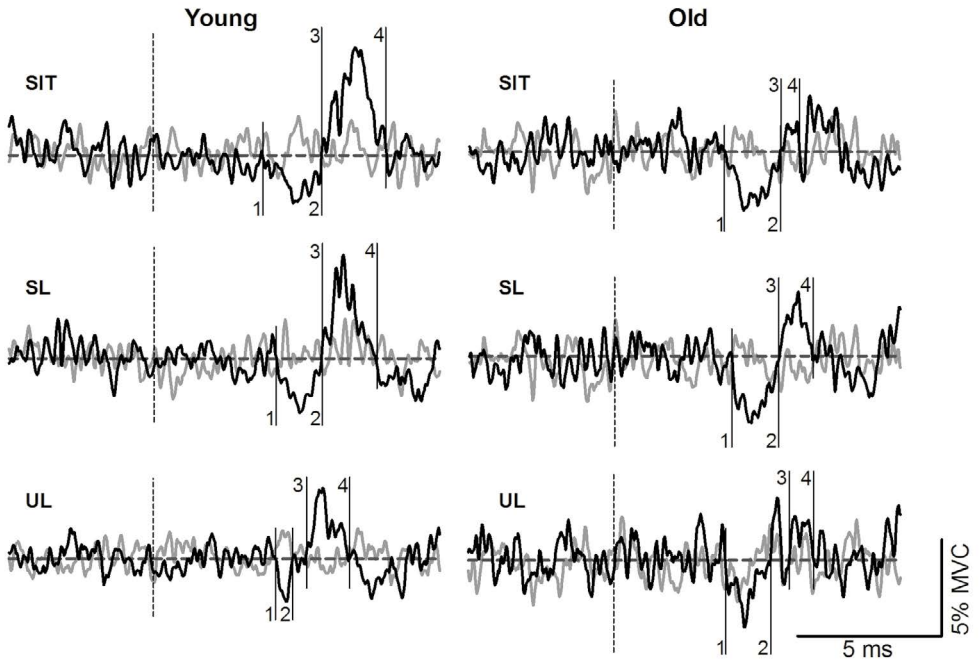


Figure 2 | Representative responses in the soleus to subthreshold transcranial magnetic stimulation (TMS) of one young (30 years) and one old (70 years) adult during sitting (SIT), supported leaning (SL), and unsupported leaning (UL). Waveforms represent rectified EMG traces averaged over 120 trials before the TMS pulse (gray line) and after the TMS pulse (black line). The horizontal dashed line represents the mean level of background EMG. The vertical lines represent the time of the TMS pulse (dashed line), the onset of EMG suppression (1), the end of EMG suppression (2), the onset of EMG facilitation (3), and the end of EMG facilitation (4).

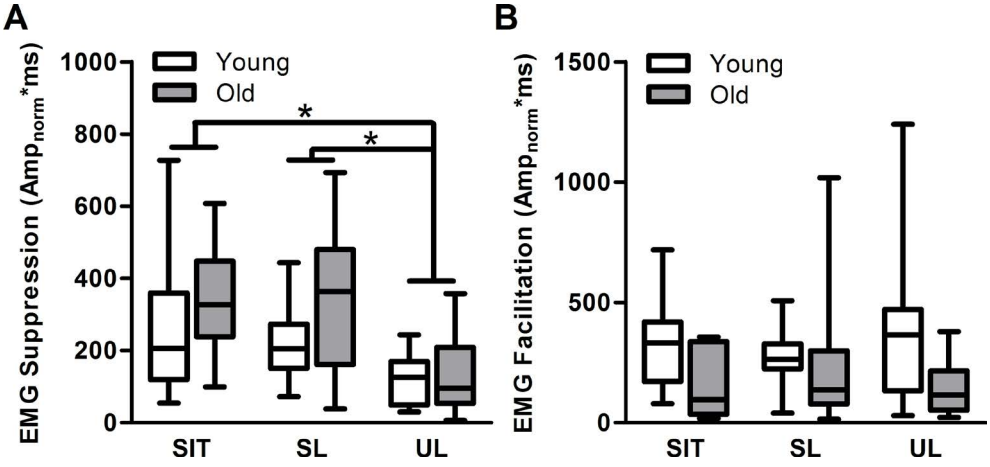


Figure 3 | Group data for young and old adults of (**A**) soleus EMG suppression, and (**B**) soleus EMG facilitation. Conditions were sitting (SIT), supported leaning (SL), and unsupported leaning (UL). The horizontal line within the box indicates the median value, the box covers the 25th–75th percentiles, and the whiskers represent the range. * denotes a significant difference ($p<0.05$).

pression ($F(1,24)=2.1$, $p=0.158$; $F(2,48)=1.7$, $p=0.188$). None of these results were affected by the addition of bEMG as a covariate.

The onset latency of EMG facilitation was 57.11.4 ms in young and 67.8±3.8 ms in old adults, with a difference of 20.3±1.4 ms in young and 26.8±3.2 ms in old adults between EMG facilitation onset and MEP onset. EMG facilitation did not change between conditions ($F(1.6, 38.6)=0.03$, $p=0.954$). There was a group effect on EMG facilitation ($F(1,24)=6.4$, $p=0.018$), with ~40% lower facilitation in old compared with young adults. There was no condition by group interaction on EMG facilitation ($F(1.6, 38.6)=0.9$, $p=0.386$). When EMG facilitation was adjusted for bEMG, there were no significant condition, group or interaction effects. In old adults, but not in young adults, EMG facilitation and suppression across all conditions were positively correlated ($r=0.48$, $p=0.003$).

As interstimulus intervals were relatively short, we tested whether the train of TMS pulses induced changes in motor cortical activity by comparing the first and last 40 trials of each condition. No significant differences were found in EMG suppression (SIT: $t(25)=-0.6$, $p=0.570$, SL: $t(24)=0.4$, $p=0.664$, UL: $t(24)=-0.2$, $p=0.881$) or EMG facilitation (SIT: $t(25)=-0.2$, $p=0.833$, SL: $t(24)=-0.3$, $p=0.779$, UL: $t(24)=-0.1$, $p=0.920$).

3.4. Correlations

Although the target lean was set at 75% of the maximum, there was still some individual variety in percentage lean, ranging from 70.2 to 79.1%. Participants leaning closer to their maximum showed less EMG suppression during UL as a percentage of EMG suppression during SL (rho=-0.44, $p=0.034$; Fig. 4), even when controlled for bEMG during UL (rho=-0.53, $p=0.012$). There was, however, no correlation between EMG suppression and leaning performance, quantified by CoP variability (rho=-0.12, $p=0.590$) and error from the target (rho=-0.14, $p=0.526$).

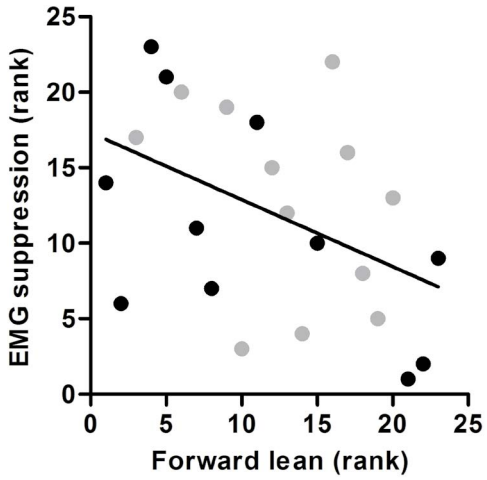


Figure 4 | Correlation between the forward lean and the EMG suppression during unsupported leaning. The forward lean was defined as the CoP position in anteroposterior direction during the unsupported leaning condition as a percentage of the CoP position during a maximum forward lean. The EMG suppression was expressed as a percentage of the EMG suppression during supported leaning. Because of non-normal distribution, the ranks are shown instead of the original data. The regression line illustrates that leaning more forward was correlated with less EMG suppression (rho = -0.44, p = 0.034). Gray and black symbols, respectively, denote young and old adults.

3.5. Fatigue

There were no signs of fatigue during the experiment. There was no change in EMG MDF during leaning before and after the experiment ($F(1,24)=2.1$, $p=0.164$) and the Borg rating of perceived exertion were low (Young: SIT: 11.0±0.6, SL: 9.5±0.7, UL: 9.6±0.5; Old: SIT: 9.7±0.7, SL: 10.0±0.7, UL: 9.1±0.5).

4. DISCUSSION

We examined age-related changes in motor cortical activity during postural and non-postural contractions in a postural challenging and non-challenging context. The main finding was a decrease in TMS-induced EMG suppression during UL compared with SL and SIT in both age groups. Moreover, leaning closer to the personal maximum correlated with a greater decrease in EMG suppression. The results suggest that postural challenge, and not contraction aim or posture, was the critical factor in modulating motor cortical activity. As quantified by the modulation in EMG suppression, age did not affect motor control strategies under the current experimental conditions, in which the task was adjusted to individual skill level.

4.1. Cortical mechanisms

The subTMS method was first described by Davey et al. [22], and subsequent experiments using a variety of techniques supported the idea that the TMS-induced EMG suppression originates from activation of intracortical inhibitory circuits, reducing motor cortical output [22,29,31,32]. For example, transcranial electrical stimulation, thought to activate the axons of the corticospinal neurons directly, does not suppress ongoing EMG [29]. Moreover, subTMS produces no recognizable descending volleys measured with high cervical, epidural electrodes [31]. Together these studies suggest that subTMS only activates motor cortical neurons with minimal or no influences from segmental circuits on the TMS-induced EMG suppression.

Changes in TMS-induced EMG suppression can be attributed to changes in the cortical contribution to the ongoing EMG or changes in intracortical inhibition [33]. When the cortical contribution to the EMG is reduced, inhibition of the corticospinal pathway will have a smaller influence on the EMG, resulting in less TMS-induced EMG suppression. Alternatively, reduced excitability of intracortical inhibitory circuits (or increased excitability of intracortical facilitatory circuits) would also result in less TMS-induced EMG suppression. We have two reasons to favor the last explanation in the current study. First, similar changes in intracortical inhibition between postural tasks have been found using paired pulse TMS [16,19,20]. Second, greater forward lean was associated with greater reductions in EMG suppression. It seems unlikely that one would reduce cortical contribution when getting closer to the boundaries of stability. We therefore propose that the modulation in TMS-induced EMG suppression found in the current study was related to mod-

ulation in intracortical circuits and not to changes in cortical contribution to the ongoing EMG.

4.2. Postural challenging and non-challenging context

Several lines of evidence suggest that the level of muscle activation may not be the only factor underlying the modulation of corticospinal excitability and intracortical inhibition. The nature of the task, i.e., how and in what context a muscle is used also seems to contribute to this modulation. For example, in exploring the basic neural processes involved in the functional linking between motor cortical points in the ketamine-anaesthetized cat, pharmacological and electrical microstimulation manipulations revealed functional connections in the recruitment of muscle synergies [34]. In healthy humans, there was a context-dependent modulation of SICI across shoulder, elbow, and finger muscles during the execution of a pointing task [35]. There was also a functional coupling between index finger and thumb muscle activation when healthy adults used these muscles synergistically, mediated at least in part by a decrease of SICI and an increase of recurrent excitation [36].

With respect to postural control, previous studies have compared contractions during sitting vs. standing to investigate the influence of contraction aim on corticospinal measures [15,16,21,37,38]. However, this method has the limitation that not only contraction aim, but also posture and postural challenge are altered. To the best of our knowledge, the present study is the first to investigate the different factors (contraction aim, postural challenge, posture) separately. The pattern of modulation in EMG suppression (less suppression during UL compared with SL and SIT) suggests that postural challenge was the most critical factor modulating motor cortical activity, whereas contraction aim and posture had no or only a small influence.

The modulation in EMG suppression between postural challenging and non-challenging contexts observed in the current study is consistent with the literature reporting a decrease in intracortical inhibition and an increase in cortical excitability with an increase in postural task difficulty [3,16,20,21]. We found that the modulation was not correlated with motor performance, but it was correlated with the CoP position in relation to the maximum forward lean. This is somewhat surprising, and suggests that it is not merely task difficulty that influences the intracortical circuits, as task difficulty would also be reflected in CoP variability. It seems that instead the modulation in motor cortical activity was related to the threat of losing balance, which increases when moving the center of mass closer to the boundaries of stability. Interestingly, changes in intracortical inhibition and cortical excitability are not always related to level of muscle contraction and are present even when the investigated muscle is relaxed [16] or, as in the present study, when muscle activity is similar between conditions [3]. Therefore, we speculate that these modulations are a reflection of an increased readiness state of the central nervous system to counteract possible oncoming perturbations. In behavioral research investigating the effect of expectation and context on postural responses to surface translations or rotations this readiness state is referred

to as "central set" [5]. Whether the modulation in intracortical circuits indeed underlies central set changes for postural responses would be an interesting topic for future research.

4.3. No age-related differences in modulation of EMG suppression

To the best of our knowledge, this is the first study using subthreshold TMS in old adults. We found no age-related differences in the modulation of EMG suppression between conditions. These results are consistent with a previous study where we used paired pulse TMS and found similar modulation of SICI between supported and unsupported standing in young and old adults [19]. However, we did find an age by condition interaction in SICI when comparing standing on foam vs. standing on a rigid platform [20]. Differences in postural challenge can explain these different outcomes. When young and old adults perform the same difficult task (standing on foam), old adults will be more unstable likely due to age-related changes in sensory input [39,40], muscle strength [41-43], and nerve conduction velocity [44]. The greater relative postural challenge might underlie the greater modulation in intracortical inhibition. In the present study we adjusted postural challenge to personal skill level, by setting the target relative to the maximum. Despite the fact that individual maxima for forward leaning were much lower in old adults, modulation of EMG suppression was similar between young and old adults. This suggests that age does not affect the motor control strategy of reducing intracortical inhibition when posture is challenged. However, the absolute threshold when modulation of intracortical inhibition is required seems to be lower.

4.4. EMG facilitation

In most subjects EMG activity became facilitated after the suppression. Similar facilitation has been reported in previous studies but the neural correlates remain unclear [22,29,33,45]. Consistent with Seifert and Petersen [33], we did not find a relationship between the magnitude of suppression and facilitation in young subjects. However, in old adults greater facilitation was correlated with greater suppression. Therefore, it seems likely that at least part of the facilitation was due to a 'rebound' effect; a synchronous discharge of the motor units after a period of inhibition [45,46]. The facilitation may also be due to activation of intracortical excitatory circuits [33,45].

4.5. Limitations and future recommendations

Although subjects received feedback in all conditions, the type of feedback differed between UL (CoP position) and SIT and SL (rectified EMG signal). As the type of feedback can influence sub-TMS induced EMG suppression [47], we cannot rule out the possibility that the type of feedback played a role in the reduction of EMG suppression during UL. However, there are two reasons why we believe this is not the case. First, Lauber et al. [47] reported greater EMG suppression during a position-controlled task when compared with a force-controlled task. Therefore, greater instead

of lower EMG suppression would be expected during UL if the modulation was due to the type of feedback. Second, the correlation between the forward lean and EMG suppression during UL cannot be explained by differences in feedback.

Another limitation is that, although the leaning target was set to each subject's maximum, old compared with young adults still exhibited higher bEMG as a percentage of MVC (21 vs 12% MVC). This was caused by lower MVC values in old adults, as the absolute bEMG was similar in the two age groups. Although contraction at 10 to 40% of MVC did not affect TMS-induced EMG suppression [33], we nonetheless compared EMG suppression using an analysis of covariance with bEMG as a covariate. The condition and age by condition interaction effects remained similar to the initial analyses. Therefore, we conclude that the age-related difference in bEMG did not affect our main results. However, the interpretation of the age main effects with respect to EMG suppression and facilitation requires caution. Future research will clarify whether the age-related differences in EMG suppression and facilitation are still present when examined during muscle contractions of similar intensity, and whether under such conditions the age-related differences in inhibition and facilitation are related to balance performance.

4.6. Conclusion

TMS-induced EMG suppression, most likely reflecting intracortical inhibition, was lower during muscle contractions to keep a forward leaning posture than during voluntary contractions while sitting and during supported leaning. This decrease was due to differences in postural challenge, and not due to differences in contraction aim (postural vs. non-postural) or posture (leaning vs. sitting). Even though in absolute terms forward lean was farther in young than in old adults, modulation of TMS-induced EMG suppression was similar between young and old adults. This suggests that age does not affect the motor control strategy of modulating motor cortical activity with increasing postural challenge, but the modulation appears at a lower task difficulty with increasing age.

REFERENCES

1. Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 1910 Apr 26;40(1-2):28-121.

2. Magnus R. Some results of studies in the physiology of posture. Lancet 1926;2:585-588.

3. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of human standing. Acta Physiol (Oxf) 2009 Mar;195(3):385-395.

4. Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A. Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. J Appl Physiol 2006 Aug;101(2):420-429.

5. Horak FB, Diener HC, Nashner LM. Influence of central set on human postural responses. J Neurophysiol 1989 Oct;62(4):841-853.

6. Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: A PET study. Hum Brain Mapp 2003;19(1):47-62.

7. Papegaaij S, Taube W, Baudry S, Otten E, Hortobagyi T. Aging causes a reorganization of cortical and spinal control of posture. Front Aging Neurosci 2014 Mar 3;6:28.

8. Ridding MC, Taylor JL, Rothwell JC. The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. J Physiol 1995 Sep 1;487 (Pt 2)(Pt 2):541-548.

9. Rantalainen T, Weier A, Leung M, Brandner C, Spittle M, Kidgell D. Short-interval intracortical inhibition is not affected by varying visual feedback in an isometric task in biceps brachii muscle. Front Hum Neurosci 2013 Mar 8;7:68.

10. Sharples SA, Kalmar JM. Modulation of cortical excitability and interhemispheric inhibition prior to rhythmic unimanual contractions. J Neurosci Methods 2012 Sep 30;210(2):178-186.

11. Ortu E, Deriu F, Suppa A, Tolu E, Rothwell JC. Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. J Physiol 2008 Nov 1;586(Pt 21):5147-5159.

12. Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 2008 Jan 15;586(2):325-351.

13. Howatson G, Taylor MB, Rider P, Motawar BR, McNally MP, Solnik S, et al. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. Eur J Neurosci 2011 Mar;33(5):978-990.

14. Sidhu SK, Cresswell AG, Carroll TJ. Short-interval intracortical inhibition in knee extensors during locomotor cycling. Acta Physiol (Oxf) 2013 Jan;207(1):194-201.

15. Soto O, Valls-Sole J, Shanahan P, Rothwell J. Reduction of intracortical inhibition in soleus muscle during postural activity. J Neurophysiol 2006 Oct;96(4):1711-1717.

16. Obata H, Sekiguchi H, Ohtsuki T, Nakazawa K. Posture-related modulation of cortical excitability in the tibialis anterior muscle in humans. Brain Res 2014 Aug 19;1577:29-35.

17. Ginanneschi F, Del Santo F, Dominici F, Gelli F, Mazzocchio R, Rossi A. Changes in corticomotor excitability of hand muscles in relation to static shoulder positions. Exp Brain Res 2005 Mar;161(3):374-382.

18. Dominici F, Popa T, Ginanneschi F, Mazzocchio R, Rossi A. Cortico-motoneuronal output to intrinsic hand muscles is differentially influenced by static changes in shoulder positions. Exp Brain Res 2005 Aug;164(4):500-504.

19. Papegaaij S, Baudry S, Négyesi J, Taube W, Hortobágyi T. Intracortical inhibition in the soleus muscle is reduced during the control of upright standing in both young and old adults. Manuscript submitted for publication 2015.

20. Papegaaij S, Taube W, Hogenhout M, Baudry S, Hortobagyi T. Age-related decrease in motor cortical inhibition during standing under different sensory conditions. Front Aging Neurosci 2014 Jun 12;6:126.

21. Baudry S, Collignon S, Duchateau J. Influence of age and posture on spinal and corticospinal excitability. Exp Gerontol 2015 Jun 6;69:62-69.

22. Davey NJ, Romaiguere P, Maskill DW, Ellaway PH. Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. J Physiol 1994 Jun 1;477 (Pt 2)(Pt 2):223-235.

23. Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002 Feb 26;58(4):630-635.

24. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008 Jan 2;28(1):91-99.

25. Baudry S, Penzer F, Duchateau J. Input-output characteristics of soleus homonymous Ia afferents and corticospinal pathways during upright standing differ between young and elderly adults. Acta Physiol (Oxf) 2014 Mar;210(3):667-677.

26. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar;49(2):M85-94.

27. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2(2):92-98.

28. Hebbal GV, Mysorekar VR. Evaluation of some tasks used for specifying handedness and footedness. Percept Mot Skills 2006 Feb;102(1):163-164.

29. Petersen NT, Butler JE, Marchand-Pauvert V, Fisher R, Ledebt A, Pyndt HS, et al. Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. J Physiol 2001 Dec 1;537(Pt 2):651-656.

30. Zuur AT, Lundbye-Jensen J, Leukel C, Taube W, Grey MJ, Gollhofer A, et al. Contribution of afferent feedback and descending drive to human hopping. J Physiol 2010 Mar 1;588(Pt 5):799-807.

31. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res 1998 Mar;119(2):265-268.

32. Classen J, Benecke R. Inhibitory phenomena in individual motor units induced by transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1995 Oct;97(5):264-274.

33. Seifert T, Petersen NC. Changes in presumed motor cortical activity during fatiguing muscle contraction in humans. Acta Physiol (Oxf) 2010 Jul 1;199(3):317-326.

34. Schneider C, Devanne H, Lavoie BA, Capaday C. Neural mechanisms involved in the functional linking of motor cortical points. Exp Brain Res 2002 Sep;146(1):86-94.

35. Devanne H, Cohen LG, Kouchtir-Devanne N, Capaday C. Integrated motor cortical control of task-related muscles during pointing in humans. J Neurophysiol 2002 Jun;87(6):3006-3017.

36. Kouchtir-Devanne N, Capaday C, Cassim F, Derambure P, Devanne H. Task-dependent changes of motor cortical network excitability during precision grip compared to isolated finger contraction. J Neurophysiol 2012 Mar;107(5):1522-1529.

37. Ackermann H, Scholz E, Koehler W, Dichgans J. Influence of posture and voluntary background contraction upon compound muscle action potentials from anterior tibial and soleus muscle following transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991 Feb;81(1):71-80.

38. Lavoie BA, Cody FW, Capaday C. Cortical control of human soleus muscle during volitional and postural activities studied using focal magnetic stimulation. Exp Brain Res 1995;103(1):97-107.

39. Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP. Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. Neurosci Biobehav Rev 2009

Mar;33(3):271-278.

40. Shaffer SW, Harrison AL. Aging of the somatosensory system: a translational perspective. Phys Ther 2007 Feb;87(2):193-207.

41. Granacher U, Gollhofer A, Hortobagyi T, Kressig RW, Muehlbauer T. The importance of trunk muscle strength for balance, functional performance, and fall prevention in seniors: a systematic review. Sports Med 2013 Jul;43(7):627-641.

42. Cattagni T, Scaglioni G, Laroche D, Van Hoecke J, Gremeaux V, Martin A. Ankle muscle strength discriminates fallers from non-fallers. Front Aging Neurosci 2014 Dec 19;6:336.

43. Hasson CJ, van Emmerik RE, Caldwell GE. Balance decrements are associated with age-related muscle property changes. J Appl Biomech 2014 Aug;30(4):555-562.

44. Nardone A, Siliotto R, Grasso M, Schieppati M. Influence of aging on leg muscle reflex responses to stance perturbation. Arch Phys Med Rehabil 1995 Feb;76(2):158-165.

45. Petersen NC, Taylor JL, Murray NP, Gandevia SC, Butler JE. Differential effects of low-intensity motor cortical stimulation on the inspiratory activity in scalene muscles during voluntary and involuntary breathing. Respir Physiol Neurobiol 2011 Feb 15;175(2):265-271.

46. Turker KS, Powers RK. Effects of large excitatory and inhibitory inputs on motoneuron discharge rate and probability. J Neurophysiol 1999 Aug;82(2):829-840.

47. Lauber B, Leukel C, Gollhofer A, Taube W. Time to task failure and motor cortical activity depend on the type of feedback in visuomotor tasks. PLoS One 2012;7(3):e32433.

CHAPTER 6

Neural correlates of motor-cognitive dual-tasking in young and old adults

S. Papegaaij

T. Hortobágyi

B. Godde

W.A. Kaan

P. Erhard

C. Voelcker-Rehage

Neuroimage 2015: Under review.

ABSTRACT

When two tasks are performed simultaneously, performance often declines in one or both tasks. These so-called dual-task costs are more pronounced in old than in young adults. One proposed neurological mechanism of the dual-task costs is that old compared with young adults tend to execute single-tasks with higher brain activation, which may reduce the residual capacity needed to perform the dual-task. The purpose of the study was to determine whether this structural interference indeed plays a role in the age-related decrease in dual-task performance. Functional magnetic resonance imaging (fMRI) was used to investigate 23 young adults (20-29 years) and 32 old adults (66-89 years) performing a calculation (serial subtraction by seven) and balance-simulation (plantar flexion force control) task separately or simultaneously. Behavioral performance decreased during the dual-task compared with the single-tasks in both age groups, with greater dual-task costs in old compared with young adults. Brain activation was significantly higher in old than young adults during all conditions. Region of interest analyses were performed on brain regions that were active in both tasks. Structural interference was apparent in the right insula, as quantified by an age-related reduction in upregulation of brain activity from single- to dual-task. However, the magnitude of upregulation was not correlated with dual-task costs. Therefore, we conclude that the greater dual-task costs in old adults were probably not due to increased structural interference.

1. INTRODUCTION

Although postural control of standing is a highly automated task, simultaneous performance of a cognitive task can interfere with the fluid execution of one or both tasks [1-4]. This decline in performance from single- to dual-task execution is called dual-task cost (DTC). Old compared with young adults exhibit higher DTC in a wide variety of motor and cognitive tasks [5-10]. Less is known about the neural mechanisms underlying the age-related changes in dual-tasking. An understanding of these neural mechanisms would strengthen the conceptual basis of interventions incorporating dual-tasking, a common practice in the promotion of old adults' health [11-14]. Fresh insights could also help to clarify the basic concept of DTC.

DTC seem to arise from a competition for limited brain resources. Just et al. [15] proposed that there is a limited amount of cortical tissue that can be activated at the same time. This was supported by their findings that the total amount of brain activation during dual-tasking (number of voxels active) was less than the sum of the single-tasks even though the single-tasks evoked only non-overlapping brain areas [15,16]. Although a limited amount of brain activation might explain a part of the DTC, the costs increase when the single-tasks require similar brain regions [17-20]. For example, visuospatial compared with non-spatial tasks affected old adults' gait more severely, probably because visuospatial working memory is also involved in gait control [20]. Furthermore, Nijboer et al. [21] reported that DTC correlated with similarity in brain activation between single-tasks measured with functional magnetic resonance imaging (fMRI). The competition for shared brain regions has been called structural interference.

There is now overwhelming evidence that old compared with young adults use expanded brain networks and increased brain activation to perform a motor or cognitive single-task [22,23]. The age-related increase in neural activation may lead to greater structural interference because of reduced residual capacity in shared brain regions, causing dual-task decrements [22,24,25]. Van Impe et al. [25] tested this hypothesis in an fMRI study using an arithmetic (i.e., serial addition by three) and a visuomotor task (i.e., circle drawing). Overlapping brain activation was located in the supplementary motor area (SMA), which was then subjected to a region of interest analysis. Although SMA activation was higher in old vs. young adults during the visuomotor task, both young and old individuals increased their brain activation from single- to dual-task performance. Therefore, there was little or no evidence for increased structural interference. However, age also did not affect DTC, suggesting that the arithmetic task was perhaps not challenging enough. Our goal was to determine whether increased structural interference underlies dual-task decrements in old adults using more challenging tasks.

Another often-debated aspect of dual-tasking is whether it requires additional brain activation that cannot be explained by the single-tasks. Some studies did find evidence for such dual-task specific activation [26-29], whereas others did not [17,30,31]. To the best of our knowl-

edge, only one study investigated dual-task specific activation in young and old adults, finding no dual-task specific activation in either of the age groups [25]. Therefore, our second goal was to determine whether there is dual-task specific activation in a challenging motor-cognitive dual-task, and if so, whether there are age-related changes in dual-task specific activation.

Dual-tasking can comprise a diverse repertoire of composite tasks, including working memory, arithmetic, visuomotor, reaction time, and balance tasks. Gait speed in combination with the ability to maintain one's balance are hallmarks of mobility in old age [32-34], and dual-task decrements in motor-cognitive balancing tasks are associated with an increased fall risk [35-38]. Therefore, we simulated active balance control in the MRI scanner using a plantar flexion force control task in the context of maintaining one's standing balance, a task that activates brain regions observed also in active and imaginary standing [39-43]. Moreover, torque variability during a seated torque-matching task correlated with torque variability during quiet standing (Kouzaki and Shinohara, 2010, Mello et al., 2013). We paired simulated balancing as a motor task with a challenging cognitive task, serial subtraction by seven, to increase dual-task challenge and induce a more robust structural interference than reported previously (van Impe et al. [25].

We hypothesized that old versus young adults would exhibit: (1) lower performance and higher brain activation during single-tasks; (2) reduced upregulation in brain activation from single- to dual-task in shared brain regions, due to the already high activation during single-tasks, accompanied by greater DTC on a behavioral level; and (3) based on van Impe et al. [25], no dual-task specific activation in either age group. A negative correlation between the magnitude of upregulation and dual-task costs would further support the hypothesis that an increase in structural interference underlies the age-related decline in dual-task performance. Based on previous imaging studies on balance control [39-41,43,44] or mental calculation [25,45-48], potential regions for structural interference were the SMA, insula, thalamus, precuneus, prefrontal gyrus, middle/inferior frontal gyri, and inferior parietal lobule.

2. MATERIALS AND METHODS

2.1. Participants

Twenty-six young female adults (mean ± SD age 23.6 ± 2.6 years, range 20 - 29) and 42 old female adults (mean ± SD age 73.9 ± 5.1 years, range 66 - 89) with no history of neurological disorders participated in the study. The old adults were recruited from an all-female database created in a previous study at our center (Niemann et al., unpublished). The young adults were recruited via advertisements at the Jacobs University and Bremen University. Before the experiment, all subjects signed an informed consent document approved by the Medical Ethics Committee of the German Association of Psychology. Three young and ten old adults were excluded from the analyses, because of technical issues (n = 4), excessive movement in the scanner (n = 1), visual

Table 1 | Subject characteristics.

	Young		Old	
	Included (n = 23)	**Excluded (n = 3)**	**Included (n = 32)**	**Excluded (n = 10)**
Age (years)	24±3 (20-29)	23±3 (21-26)	74±5 (66-89)	75±4 (69-81)
MoCa score	-	-	26±3 (21-30)	26±2 (23-30)
One leg stance time (s)	19.8±1.0 (15.4-20.0)	18.3±2.9 (15.0-20.0)	6.0±2.7 (2.1-11.6)	7.8±5.2 (3.9-20.0)
Years of education	17±2 (14-21)	17±1 (16-18)	14±3 (8-19)	13±2 (10-15)

Values are mean ± SD, with the range between brackets. MoCa: montreal cognitive asessment (max. score of 30).

problems (n = 1) or calculation below chance level (n = 7). Table 1 shows the characteristics of the included and excluded participants. The Montreal Cognitive Assessment (MoCa) was administered to assess cognitive functioning in the old adults. To test standing balance, we recorded one leg stance time (maximum 20 seconds) with the eyes closed [49] and averaged the best of two trials for left and right. Results from this test were used to test the external validity of the simulated balance task in the fMRI.

2.2. Experimental setup

Participants lay supine in the MRI scanner with their feet against a custom-made force platform attached to the MRI bed (Fig. 1A). The position of the force platform was adjusted to subject

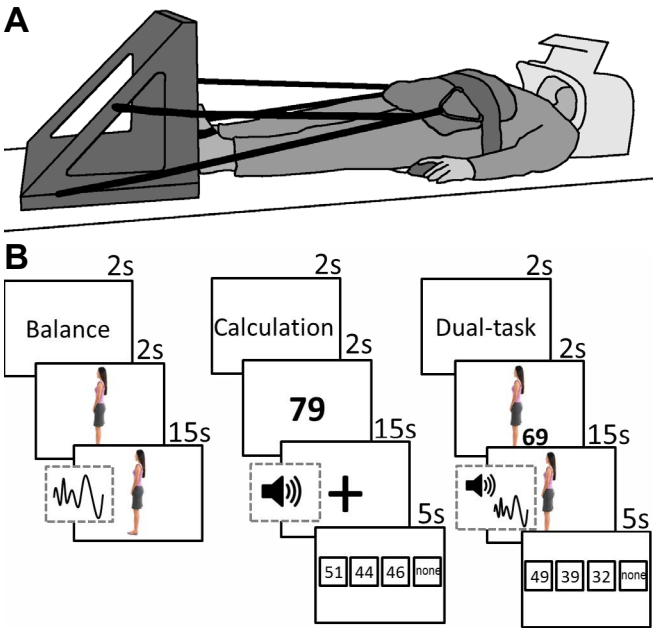


Figure 1 | A Illustration of experimental setup in the scanner. Participant lies supine with her feet against the force platform. **B** Schematic of the stimuli during balance, calculation and dual-task conditions. The sine wave signifies the addition of the disturbance signal, causing the avatar to sway forward and backward. The speaker signifies the addition of beeps, which indicated the time points at which the participant had to subtract.

height via a sliding mechanism. The force platform consisted of a sturdy plastic board connected to a load cell (Vishay Tadea-Huntleigh Model 1402, Oisterwijk, the Netherlands) positioned between the two feet at the height of the first metatarsophalangeal joints. The feet were affixed to the force platform by Velcro straps. To simulate weight-bearing and avoid excessive head movement, participants were pulled towards the force platform using thick elastic ropes attached to a hip belt (C.P. Sports Ultraleichtgürtel, Germany). The amount of axial load was set to 70 - 80 N. A four-button device was placed underneath the right hand for the calculation task.

We created a virtual instrument using National Instruments LabVIEW 2013 (13.0.1f2) to acquire the force data with a sample frequency of 100 Hz, and display the tasks to the participants. The tasks were projected onto a white screen placed at the head of the scanner. Participants could see the screen via a mirror attached to the head coil.

2.3. Tasks

During the balance task, an avatar in the shape of a woman was displayed on the screen. The avatar swayed forward and backward. Participants were instructed to try to keep the avatar in the upright position by increasing or decreasing the level of plantarflexion force measured by the load cell. As in normal standing, increasing the plantarflexion force led to a backward sway, and vice versa. The avatar was upright at a force of 75 N and swayed with 1.8°/N. These numbers were chosen based on pilot data to minimize head movement while still requiring active force control. Force data were filtered online with a 10-point moving average filter. At the start of every balance condition, participants were given two seconds to bring the avatar in the upright position. After these two seconds, a disturbance signal was added, causing the avatar to sway forward and backward. In order to keep the avatar upright, participants had to counteract these disturbances. The disturbance signal was made by combining fifteen sinusoidal signals with random phases and with frequency characteristics based on an average frequency spectrum of Center of Pressure movement during upright standing (0.025 – 1 Hz), measured in ten young and ten old adults. The maximum amplitude of the disturbance was ±30°.

The calculation task consisted of serial subtractions with increments of seven. At the start, a number between 50 and 100 was projected on the screen for two seconds. Every participant received the same set of start numbers. Then, a plus sign was displayed on the screen and every 3 to 4 seconds a beep was generated through an MRI compatible headphone (MR confon Optime 1, Magdeburg, Germany), with a total of four beeps per trial. Participants were instructed to subtract seven at every beep. At the end, four answer possibilities were given, always including the correct answer, two erroneous answers, and the option that none of the other answers are correct. Participants indicated which answer they thought was correct by pressing the corresponding button of the four-button device.

During the dual-task condition, subjects performed the balance and calculation tasks si-

multaneously. They were instructed to do both tasks as well as possible. All participants received a short practice session outside of the MRI scanner and again in the scanner, to make sure that the instructions were understood.

2.4. Experimental design

An fMRI block-design was used to alternate between the three conditions: balance, calculation, and dual-task. Every participant performed twelve blocks of each condition, 36 blocks in total, with the order of the conditions balanced across blocks and randomized between subjects. At the end of every block a 15-second rest period was given. Fig. 1B illustrates the time frame of the visual stimuli per condition.

2.5. Behavioral data analysis

Performance on the balance task was quantified as the root-mean-square error (RMSE) angle between the avatar and the vertical, averaged across blocks. Performance on the calculation task was quantified as the percentage of correct answers (%correct). DTC were calculated for the balance and calculation tasks using the following formula [25]:

$$\mathrm{DTC} = \frac{\mathrm{Performance(single-task)} - \mathrm{Performance(dual-task)}}{\mathrm{Performance(single-task)}} \times 100$$

High DTC scores denote a great performance decline from single- to dual-task. Mean DTC were calculated by averaging the DTC for the balance and calculation tasks [50].

2.6. Statistical analysis

All behavioral variables (RMSE, %correct, mean DTC) were checked for outliers using the outlier labeling rule [51] with a multiplier of 2.2 as suggested by Hoaglina & IgleWiczb [52]. Mean DTC in two young participants were identified as outliers and these data points were excluded from further analyses. An age (young, old) by condition (single-task, dual-task) mixed ANOVA was performed on RMSE and %correct. An independent t-test was used to test differences in mean DTC between young and old adults. To test the external validity of the balance simulation task, a Pearson correlation coefficient was calculated between RMSE during the balance condition and one leg stance time in old adults. The alpha level was set at 0.05.

2.7. fMRI data acquisition

Brain imaging was performed on a 3-T SIEMENS Magnetom Skyra System (Siemens, Erlangen, Germany) with a 20 channel head/neck coil. For functional scans, A T2*-weighted multiband gradient echo-planar imaging (EPI) sequence was used (TR = 700 ms, TE = 30 ms, flip angle = 55°, 48 axial slices, slice thickness = 3 mm, no gap, in-plane resolution 3x3 mm) [53]. After the functional scanning session, a high resolution magnetization prepared rapid acquisition gradient

echo (MPRAGE) T1-weighted sequence (TR = 2100 ms, TE = 4.6 ms, TI = 900 ms, flip angle = 8°, 192 contiguous slices, voxel resolution 1 mm^3, FOV = 256x256x192 mm, iPAT factor of 2) was obtained in sagittal orientation. These anatomical scans were used to co-register the functional runs.

2.8. fMRI data analyses

2.8.1. Preprocessing

All fMRI data analyses were performed using the statistical parametric mapping software SPM 12 (Welcome Department of Cognitive Neurology, London, UK), implemented in Matlab R2014b (Mathworks, Natick, MA). For each subject, we corrected for inter-scan movement using the realign and unwarp option with the first scan as a reference. The anatomical scan was segmented using the SPM tissue probability maps. All functional scans were co-registered to the anatomical scan and normalized to the Montreal Neurological Institute (MNI) template brain via the forward deformations revealed by the segmentation. The normalized images were smoothed using an 8-mm FWHM Gaussian kernel.

2.8.2. First level fMRI analysis

All analyses were performed using the General Linear Model. Each condition was modeled with a boxcar function convolved with canonical hemodynamic response functions (HRF). Also the pre- and post-condition episodes (condition announcement, start balance, number display, button response) were separately entered into the model. The motion parameters obtained from the realignment step were used as covariates. A high-pass filter (1/277 Hz) was applied to remove low-frequency signal drifts and a first-order autoregressive model was fit to the residuals to account for temporal correlations. For each subject, condition (balance, calculation, dual-task) vs. baseline contrasts were computed.

2.8.3. Group level fMRI analysis

The first-level contrasts were subjected to a random-effects analysis. A 2x3 full factorial design was used with age-group as between-subjects factor (young, old) and condition as within-subjects factor (balance, calculation, dual-task). Brain activation associated with each condition was assessed by computing the simple effects. Age effects on brain activation were assessed by computing the t-contrasts 'young vs. old' and 'old vs. young' for each condition. The statistical threshold was set at $p < 0.05$, family wise error (FWE) corrected at the voxel level. Brain regions were labeled using automated anatomical labeling [54].

To test whether age-related changes in activation were related to performance, we performed regression analyses with brain activation associated with balance, calculation or dual-tasking as dependent variable and single-task performance and mean DTC as covariates of interest ($p < 0.001$ uncorrected, extend threshold of 10 voxels). The corresponding 'young > old'

and 'old > young' contrasts ($p < 0.001$, uncorrected) were used as inclusive masks.

To test whether dual-tasking required additional activation of brain regions that cannot be explained by the single-tasks, we calculated the contrast suggested by Szameitat et al. [55] per age group. This contrast subtracts the sum of the single-task activations from the dual-task activation. The contrast 'dual-task > baseline' was used as an inclusive mask ($p < 0.001$, uncorrected). Significant differences were recognized at $p < 0.05$, FWE corrected.

To find the brain regions with potential structural interference between balancing and calculation, we performed a conjunction analysis with four contrasts: 'balance vs. baseline' and 'calculation vs. baseline' for young and old adults ($p < 0.05$, FWE corrected). These brain regions were subjected to a ROI-analysis. To minimize the number of ROI-analyses, the extent threshold was set at ten voxels. We extracted the beta values from the individual peak voxels for the conjunction analysis within every ROI. An age (young, old) by condition (balance, calculation, dual-task) repeated measures ANOVA was performed for every ROI to see if there were any age by condition interaction effects. In case of violation of the assumption of sphericity, a Greenhouse–Geisser correction was applied. The Bonferroni method was used to correct for multiple comparisons. Post-hoc analyses were done only in the ROI's showing a significant age by condition interaction. As we expected that old adults would show increased activation during single-tasks and therefore less residual capacity to upregulate the activation for the dual-task, we were interested in the activation upregulation from single- to dual-task. Using the extracted beta values, we calculated the upregulation from balance to dual-task and from calculation to dual-task as follows:

$$\text{Upregulation} = \frac{\text{BOLD(dual-task)} - \text{BOLD(single-task)}}{\text{BOLD(single-task)}} \times 100$$

We also calculated the mean upregulation by averaging the upregulation from balance to dual-task and from calculation to dual-task. Outliers were detected according to the outlier labeling rule (cf. above) and excluded from analysis (4% of all data points). Independent t-tests were used to compare the upregulation between age groups for each ROI. P-values were corrected for multiple comparisons. Pearson correlations were computed between mean upregulation and mean DTC.

3. RESULTS

3.1. Behavioral data

Fig. 2A shows the group data for the performance on the balance task during the balance-only task and balance plus calculation dual-task. Balance performance was significantly worse during dual- vs. single-tasking, as shown by a 7% increase in RMSE ($F(1,53) = 9.0$, $p = 0.004$, $= 0.15$). Across conditions, RMSE was 41% higher for old compared with young adults ($F(1,53) = 18.7$, $p < 0.001$, $= 0.26$). There was no significant age x condition interaction in RMSE ($F(1,53) = 0.5$, $p =$

0.504, = 0.01). RMSE during balance did not correlate with one leg stance time (young: r = 0.14, p = 0.516; old: r = -0.03, p = 865).

Fig. 2B shows the data for the percent of correct calculation trials during single- and dual-tasking. Overall, similar to balancing, the calculation performance decreased by 7% between dual- and single-tasking ($F(1,53) = 5.5$, $p = 0.022$, $= 0.10$) and was 17% lower in old vs. young adults ($F(1,53) = 9.3$, $p = 0.003$, $= 0.15$). Again, there was no significant age x condition interaction ($F(1,53) = 2.6$, $p = 0.111$, $= 0.05$).

Mean DTC were calculated by averaging the performance decline from single- to dual-tasking for the balance and calculation task. Mean DTC were significantly higher in old (9%; 9% for both balance and calculation) than in young adults (2%; 6% for balance, -1% for calculation) ($t(49) = -2.1$, $p = 0.037$, $r^2 = 0.10$, Fig. 2C).

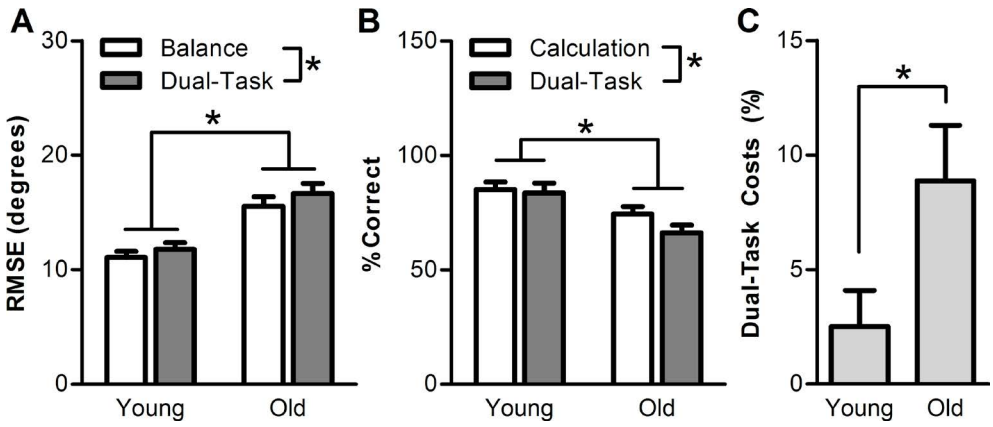


Figure 2 | Behavioral group data for young and old adults, showing the root-mean-square error (RMSE) angle between the avatar and the vertical during balance and dual-tasking (**A**), percentage trials with a correct answer on the calculation task during calculation and dual-tasking (**B**), and performance decline from single- to dual-tasking, averaged over the balance and calculation tasks (**C**). The horizontal line within the box indicates the median value, the box covers the 25th–75th percentiles, and the whiskers represent the 5th-95th percentiles. Asterisks denote statistical significance ($p<0.05$).

3.2. Condition effect on neuroimaging data

Table 1 lists the local maxima of activated clusters during balance, calculation and dual-task conditions. Figure 3A shows activation and deactivation patterns as compared to baseline. Deactivation patterns are described in more detail in the supplementary material. Main areas that were activated during balance were the bilateral MT/V5 areas (on the border between middle temporal gyrus and middle occipital gyrus), motor areas (SMA, bilateral precentral gyri), somatosensory areas (postcentral gyri, paracentral lobules, supramarginal gyri), frontal areas (middle and inferior frontal gyri), subcortical areas (cerebellum, caudate nucleus, putamen, thalamus), and the insular cortices. Deactivations were evident mainly in occipital areas (left cuneus, bilateral

Table 2 | Brain activation.

AAL location	Side	Dual-task				Balance				Calculation			
		MNI coordinates			t-value	MNI coordinates			t-value	MNI coordinates			t-value
		x	y	z		x	y	z		x	y	z	
Superior frontal gyrus (orbital part)	L	-21	51	-9	5								
Superior frontal gyrus	R									27	3	54	11.3
Middle frontal gyrus	L	-24	0	54	13.9	-36	33	33	5.4	-24	3	54	14.4
	R	39	-3	60	13.9	39	-6	57	17				
Inferior frontal gyrus (pars opercularis)	L	-57	6	18	11.3	-54	6	18	11.2				
	R	51	12	12	9.3	54	12	12	15.6				
Inferior frontal gyrus (pars triangularis)	L									-42	30	27	11.9
	R									42	33	30	10.9
Insula	L	-30	24	3	11.7	-45	3	6	12.6	-30	24	3	12.9
	R	33	21	6	13.4	45	12	0	12.4	33	24	6	13.2
Midcingulate area	L					-12	-24	45	9.9				
	R					12	-24	45	9.2				
Precentral gyrus	L	-39	-6	54	15.4	-39	-9	54	15	-45	6	33	16.7
	R	42	0	45	11	57	6	30	15.7	57	3	21	6
SMA	L	-3	-6	66	13.8	-3	-12	66	20	-3	9	54	17.6
	R	3	12	51	17.2								
Paracentral lobule	L	0	-21	69	12.7	0	-21	69	21.8				
	R					9	-39	66	12.7				
Postcentral gyrus	L	-48	-18	33	6.2	-33	-39	57	11.8				
	R	30	-36	54	8.5	30	-36	54	14.2				
Superior parietal lobule	L	-27	-63	51	13.7					-27	-63	51	15.6
	R	30	-51	57	10.5	30	-48	57	13				
Inferior parietal lobule	L	-42	-39	42	15.6					-42	-39	42	17.4
	R	39	-39	45	10.2					48	-36	48	11
Rolandic operculum	R	42	-27	21	6.5								
Precuneus	L									-12	-69	57	10.9
	R	12	-69	54	8.1					12	-66	54	8.4
Supramarginal gyrus	L	-48	-36	24	8.9	-48	-33	24	12.9				
	R					57	-30	27	15				
Superior temporal gyrus	L	-60	-39	15	10.2					-60	-39	12	9.8
	R	60	-39	18	10.7					57	-36	12	7.2
Middle temporal gyrus	L									-54	-45	-12	7.5
	R	45	-66	6	17.4	48	-69	3	24.6				

Table 2 | Continued.

Inferior temporal gyrus	L	-51	-60	-9	10.1					-51	-57	-9	9.6
	R					42	-54	-15	15.6	57	-48	-12	7.3
Superior occipital gyrus	L					-24	-75	33	5.9				
Middle occipital gyrus	L	-42	-72	6	12.8	-45	-72	3	20.5				
	R	30	-72	30	7	30	-72	30	10.1				
Thalamus	L					-12	-15	9	6.2				
	R					12	-15	9	8.1				
Brain Stem						6	-27	-36	5.4				
Caudate nucleus	L	-12	-6	15	8.3	-12	-6	15	6.3	-15	-3	15	7.1
	R	15	-6	18	8.9					15	-6	18	6.6
Putamen	L	-18	6	9	8	-27	-3	9	10.8	-21	9	6	6.9
	R	27	-9	12	5.6	30	0	9	9.1				
Globus pallidum	R	15	0	0	6.3								
Cerebellum (lobule 3)	R	15	-36	-24	6.6	15	-36	-24	9.2				
Cerebellar vermis (lobule 4-5)		0	-48	-6	9.8	0	-48	-6	10	0	-54	-15	7
Cerebellum (lobule 4-5)	L	-15	-36	-24	9	-15	-36	-24	11.4				
	R	30	-33	-33	8.4	30	-36	-30	8.5				
Cerebellar vermis (lobule 6)		6	-75	-18	12.4	0	-72	-18	7.3				
Cerebellum (lobule 6)	L	-33	-57	-27	12.4	-33	-51	-27	13	-33	-57	-30	11.7
	R	33	-69	-24	12.9	18	-69	-21	6.2	33	-69	-24	13.5
Cerebellar vermis (lobule 7)		0	-72	-33	11.2								
Cerebellum (lobule 7b)	L					-12	-72	-45	11.5				
Cerebellar vermis (lobule 8)						6	-72	-42	10.5				
Cerebellum (lobule 8)	L	-30	-63	-45	9.3	-33	-51	-51	9.9	-30	-66	-48	8.6
	R	24	-69	-48	8.1	30	-42	-48	7.7	24	-69	-48	9.3
Cerebellum (lobule 9)	L	-15	-51	-42	5.1	-15	-48	-51	9				
Cerebellum (lobule 10)	L	-27	-36	-42	7.7								
Cerebellar hemisphere (crus I)	L									-36	-42	-36	5.2
Cerebellar hemisphere (crus II)	L									-6	-75	-30	8.5
	R									6	-75	-33	8.1

MNI coordinates and t-values of the local maxima with significant activation during balance, calculation and dual-tasking ($p < 0.05$; FWE corrected for multiple comparisons). Voxel size is 3x3x3 mm.

Table 3 | Age-related differences in brain activation.

AAL location	Side	Dual-task				Balance				Calculation			
		MNI coordinates			t-value	MNI coordinates			t-value	MNI coordinates			t-value
		x	y	z		x	y	z		x	y	z	
Young > Old													
Supplementary motor area	L									0	12	45	4.8
Precentral gyrus	L									-54	9	33	5.8
Old > Young													
Medial frontal gyrus	L	0	57	6	5.1					0	57	6	6.6
Precentral gyrus	L	-24	-24	60	5.3					-45	-12	27	5.8
	R	39	-18	66	6.3	15	-27	69	5.3	39	-18	63	5.8
Paracentral lobule	L	-9	-33	78	4.8	-9	-30	72	5.6				
Postcentral gyrus	L	-48	-12	27	4.9					-39	-15	39	5
Precuneus	L	-3	-45	72	5.3	-3	-42	72	5.8				
	R					3	-63	63	5.6				
Angular gyrus	R									42	-54	27	4.9
Supramarginal gyrus	L	-63	-24	24	5					-63	-24	24	5.3
Superior temporal gyrus	L	-63	-15	3	4.9								
Middle temporal gyrus	L	-45	-60	15	5.2					-45	-60	15	5
Middle occipital gyrus	L	-42	-78	24	5								
	R	42	-72	18	5.4								
Inferior occipital gyrus	R	48	-66	-15	6.6								
Calcarine sulcus	L	3	-93	-6	5.1								
Lingual gyrus	L	-3	-87	-15	5.6								
	R	12	-93	-9	5.3								
Cuneus	L					-3	-93	15	5.5				
	R					9	-93	15	5.3				
Fusiform gyrus	R									48	-63	-18	5.6
Cerebellum (Crus I)	L									-12	-90	-21	4.9

MNI coordinates and t-values of the local maxima with significant age-related differences in activation during balance, calculation and dual-tasking ($p < 0.05$; FWE corrected for multiple comparisons). Voxel size is 3x3x3 mm.

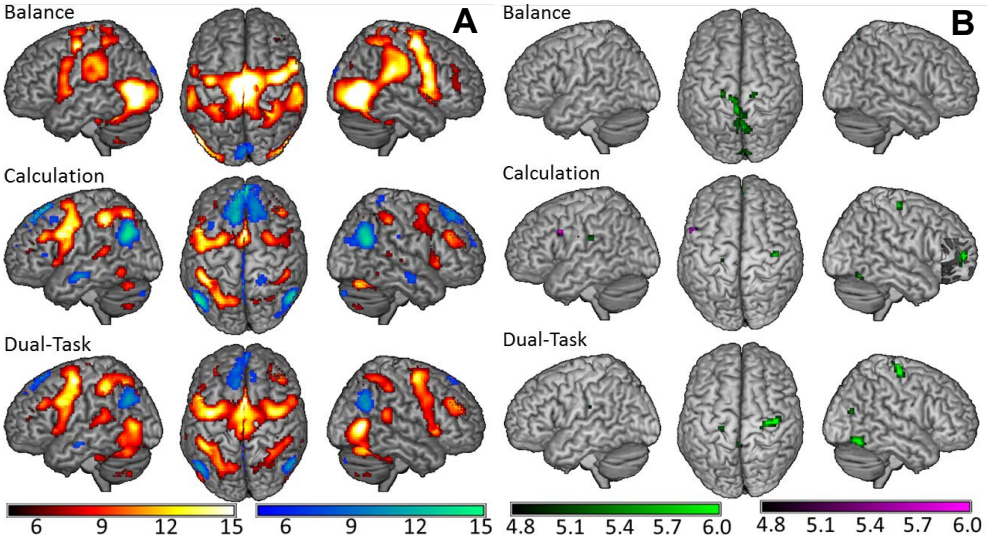


Figure 3 | Mean brain activation and deactivation patterns (**A**) and age-related differences (**B**) during balance, calculation, and dual-tasking as compared with baseline. Significant activated voxels are shown in hot colors (red/yellow), whereas significant deactivated voxels are shown in cold colors (blue/green). Voxels with higher activation in old compared with young adults are shown in green, whereas voxels with higher activation in young compared with old adults are shown in purple. Statistical significance was set at $p < 0.05$, FWE corrected for multiple comparisons.

calcarine sulci, and left lingual gyrus).

During calculation, a large fronto-parietal network was activated, including the left SMA, bilateral precentral gyri, bilateral inferior and left superior parietal lobules, left middle frontal gyrus, right superior frontal gyrus. Also bilateral insular cortices, temporal gyri, caudate nuclei and parts of the cerebellum were active. During calculation widespread areas became deactivated, including bilateral medial and superior frontal areas, bilateral angular gyri, left cingulate gyrus, left superior and bilateral middle occipital gyri, and temporal areas.

Dual-tasking evoked an activation pattern combining those of the calculation and balance task and a deactivation pattern similar to that during calculation.

3.3. Age effect on brain activation

Table 2 and Figure 3B display the local maxima of clusters with significant different activations between young and old adults. During balance and dual-tasking, there were no brain regions for which the young adults showed higher activation than the old adults. However, during calculation, more activation was observed in the left precentral gyrus and SMA for young than for old adults.

In all three conditions, there were clusters with significantly higher activation in old as compared with young adults. During balance, old adults showed higher activation in motor (right precentral gyrus and left paracentral lobule) and sensory regions (bilateral precuneus and cu-

neus). During calculation, main clusters with age-related activation increases were found in the bilateral precentral gyri and the left medial frontal gyrus. These areas were also more activated in old adults during dual-tasking. Additionally, bilateral lingual gyri, right inferior and middle occipital gyrus, left calcarine sulcus, and left precuneus were more activated in old than in young adults during dual-tasking. Bar plots of the BOLD responses in the clusters with an age-related increase in activation during dual-tasking can be found in the supplementary material. Using a multiple regression model, there were no significant relationships between brain activation and behavioral performance (single-task performance and DTC) in the brain regions showing age-related changes in brain activation.

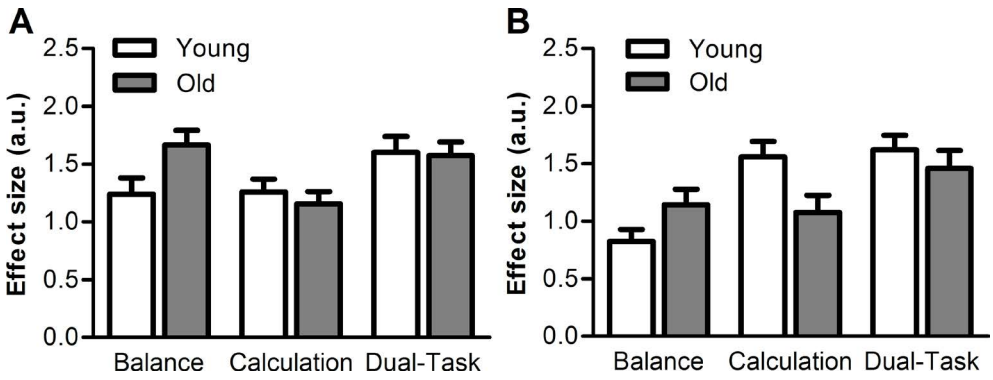


Figure 4 | Group data for young and old adults, showing the mean ± standard error of the BOLD response (in arbitrary units) during balance, calculation, and dual-tasking, in the right insula (A) and left inferior parietal lobule (B).

3.4. Structural interference

A conjunction analysis revealed eight clusters that were activated during both single-tasks in both age groups, including the SMA, right insula, bilateral premotor areas, cerebellum, and parietal lobules (Table 3). These clusters were subjected to a ROI-analysis. After multiple comparisons correction, there was a significant condition effect in all ROI's ($p < 0.024$) but no significant age effect in any of the ROI's ($p > 0.104$). The age by condition interaction was significant in two ROI's: the right insula ($F(2,83) = 7.0$, $p = 0.024$) and the left inferior parietal lobule ($F(1,68) = 9.4$, $p = 0.008$) (Fig. 4). In the right insula, there was less upregulation from balance to dual-task in old compared with young adults ($t(27) = 2.9$, $p = 0.021$). There was no difference in upregulation from calculation to dual-task between young and old adults ($t(51) = -1.6$, $p = 0.363$). Mean upregulation from single to dual-task was reduced with age ($t(52) = 3.2$, $p = 0.009$). In the left inferior parietal lobule, there was less upregulation from balance to dual-task ($t(50) = 3.0$, $p = 0.012$), but more upregulation from calculation to dual-task ($t(47) = -4.9$, $p = 0.002$), in old compared with young adults. Here, mean upregulation was not different between age groups ($t(51) = 0.4$, p

Table 4 | Conjunction balance and calculation.

AAL location	Side	Cluster size	MNI coordinates			t-value	Age x Condition	
			x	y	z		unc. P-value	corr. P-value
R middle frontal gyrus	R	136	30	0	57	6.8	0.069	0.552
Precentral gyrus	R		39	0	42	6.5		
Inferior frontal gyrus (pars opercularis)	R		45	9	30	5.3		
Precentral gyrus	L	233	-54	6	18	7.7	0.174	1
Superior frontal gyrus	L		-24	-6	57	6.1		
Inferior frontal gyrus (pars opercularis)	L		-48	9	6	5.7		
Superior frontal gyrus	L		-24	-3	69	5.3		
R insula	R	61	33	18	6	6.9	0.003*	0.024*
Supplementary motor area	L	145	0	0	60	7.8	0.06	0.48
	R		3	6	54	7.7		
Superior parietal lobule	L	52	-42	-42	57	5.8	0.001*	0.008*
Inferior parietal lobule	L		-48	-33	42	5.6		
Inferior parietal lobule	R	62	48	-36	48	6	0.007*	0.056
Cerebellum (Lobule VI)	R	12	36	-54	-27	6.1	0.816	1
Cerebellum (Crus I)	L	22	-36	-54	-30	6.8	0.163	1

MNI coordinates and t-values of the local maxima from the conjunction of the balance and calculation contrasts. Cluster size is given for the peak voxel per cluster. Voxel size is 3x3x3 mm. P-values for the age (young, old) by condition (balance, calculation, dual-task) interactions are given, with and without Bonferonni correction. * denotes significant interaction with $p < 0.05$.

= 1.000). There were no correlations between mean upregulation in the right insula or left inferior parietal lobule and mean DTC in young ($p > 0.185$) or old ($p > 0.379$) adults.

3.5. Dual-task specific activation

Table 2 shows that the great majority of the brain regions involved in dual-tasking are also involved in balance or calculation, suggesting little to no dual-task specific activation. Indeed, when contrasting the dual-task condition with the sum of the single-task conditions, there were no significant clusters in either age group.

4. DISCUSSION

We aimed to determine whether increased structural interference and/or dual-task specific activation underlies age-related dual-task decrements in the context of a balance task. As expected,

we found greater dual-task costs (DTC), increased brain activation, and decreased upregulation in old compared with young adults. However, measures of brain activation and behavior did not correlate. We found no dual-task specific activation in either group. Therefore, under the current experimental conditions, neither structural interference nor dual-task specific activation could explain the age-related increase in DTC.

4.1. Neural correlates of single-tasks

Activity patterns for the balance and calculation tasks were comparable to those reported in literature. Imaging studies have often used arithmetic tasks and, as in the present study, consistently observed an increase in activation (as compared to baseline) of the frontal-parietal network [45,47,48]. Previous studies investigating the neural correlates of balance have used fMRI during mental imagery [41,43], action observation [43], or a plantar flexion force control task [39], or PET-scans during actual standing [40]. Commonly activated areas consistent with the present study were the premotor cortex, prefrontal cortex, inferior and middle frontal gyrus, SMA, cerebellum, basal ganglia, thalamus, visual cortex, insula, and inferior parietal areas. The brain activation pattern we observed during the simulated balance task was remarkably similar to the activation pattern reported by Taube et al. [43] during the imagery and action observation of balancing, suggesting that perhaps our participants imagined themselves being the balancing avatar. Although our balance simulation task did evoke brain activation in regions known to be involved in balance, behavioral performance on this task did not correlate with one-leg-stance time. Whereas one-leg-stance time relies mainly on sideways balance [56], our simulated balance task was only in the frontal plane. As the different directions of control might have affected the correlation, the external validity of the balance task requires further investigation.

4.2. Increased brain activation in old adults

Consistent with previous fMRI studies [42,57-64], old adults exhibited greater brain activation than young adults in all tasks. Regarding balance tasks, Zwergal et al. [42] reported positive correlations between age and activation in several multisensory areas during imaginary standing compared with lying. We found age-related activation increases in both motor (precentral and paracentral gyri) and sensory (cuneus and precuneus) areas during the balance condition, possibly because our balance simulation was a real motor task instead of an imaginary motor task. During the calculation condition, the greatest cluster with an age-related increase in activation was located in the medial frontal gyrus. This area belongs to the prefrontal gyrus, in which age-related increases in activation during performance of cognitive tasks are well-known [57,65].
The functional meaning of the increased brain activation with aging is still debated [23]. One theory is that old adults use the additional activation to compensate for structural and functional decline, predicting a positive correlation between activation and behavioral performance. Al-

ternatively, the dedifferentiation theory suggests that the more widespread activation pattern results from an age-related loss in the ability to selectively recruit brain areas. Consistent positive correlations between higher prefrontal activity and cognitive performance [66-69], as well as higher brain activity in various motor, parietal, frontal and cerebellar areas and motor performance [61,70], strongly support the compensation theory. However, less neural specificity in visual areas for different stimulus categories (faces, houses, pseudowords, and chairs) in old compared with young adults [71], and negative correlations between age-related activation increases in ipsilateral motor areas and motor performance [62,63,72], show that at least in certain areas dedifferentiation occurs. Similar to van Impe et al. (2011), we found no correlation between activation in the areas over-activated by old adults and single-task performance, implying that the additional activation did not impair nor improve performance. This suggests an age-related spreading of brain activity without functional meaning, favoring the dedifferentiation over the compensation theory.

4.3. Structural interference

Regardless of the functional meaning, we hypothesized that the higher activation in old adults would cause structural interference and therefore greater DTC. However, we found no correlation between brain activation and DTC in the areas with age-related differences in activation. There are at least three possible explanations for this lack of correlation. First, the increased activation in old adults did not cause increased structural interference because the areas with higher activation were involved in only one of the two tasks. Second, old adults could still increase their brain activation from single- to dual-task, despite increased activation during single-tasks. Third, DTC were not related to structural interference.

To examine whether old adults exhibited greater structural interference, we performed a series of ROI analyses. Eight brain regions were selected because of their involvement in both tasks in both age groups. All regions, except the cerebellum, were expected to be activated in both tasks based on literature. We found an age-related increase in structural interference in the right insula, quantified as a reduced activation-upregulation from single- to dual-task. However, the amount of upregulation was not correlated with DTC, suggesting that dual-task performance was not affected by the structural interference. It may be that the age-related increase in structural interference in the right insula was too small to cause DTC, or that insular activation was not essential for task performance. Although that would explain the lack of correlation between upregulation and DTC, the observed increase in DTC with aging remains unexplained. Therefore it seems that, at least under the current experimental conditions, age-related increases in DTC were not due to greater structural interference.

4.4. Dual-task specific activation

The literature is inconsistent regarding dual-task specific activation: whereas some studies did find evidence for dual-tasking requiring activation additional to the sum of the single-tasks [26-29,73-75], others did not [17,25,30,31]. Probably, the dual-task specific activation is dependent on the single-tasks, and there is no common executive control system that is active for all types of dual-tasking [21,76]. In the current study, we did not find any dual-task specific activation in young or old adults. Therefore, it is unlikely that the age-related dual-task performance deficits were due to inadequate dual-task specific activation.

4.5. Alternative theories

As neither structural interference nor dual-task specific activation could explain the age-related deficit in dual-task performance, we must consider alternative theories that could not be tested with the current experimental setup. One theory explaining DTC is the cross-talk model [77]. Cross-talk occurs when the effects of processing one task interfere with processing the other, and is therefore dependent on the content-based overlap between tasks and stimulus-response modalities [78,79]. For example, DTC increased when the non-target words in one visual search task belonged to the target category in the other visual search task [78]. We believe that cross-talk was not a critical element in our experiment, as the tasks used did not have any content-based overlap, or incompatible or shared stimulus-response modalities. Moreover, there is no reason to think that age would affect the amount of cross-talk.

Another theory for DTC is that there is a central bottleneck that can perform certain processes only sequentially, resulting in serial queuing and time delays [80]. There is quite convincing evidence from behavioral and time-resolved fMRI studies that a central bottleneck is indeed present when two discrete choice reaction time tasks are performed with a short interstimulus interval [77,81,82]. It is possible that also during continuous tasks certain processes cannot be performed in parallel, requiring subjects to rapidly switch between tasks. As aging is associated with reduced processing speed, time delays may be more pronounced and interfere with smooth performance. Although evidence is lacking for healthy old adults, in multiple sclerosis patients processing speed indeed correlated with DTC when performing a cognitive task during gait or standing [83,84]. To determine whether a central bottleneck can account for the age-related decline in dual-task performance, future research should use high-temporal resolution measures, such as time-resolved fMRI.

4.6. Conclusions

We hypothesized that the age-related increase in brain activation during single-tasks would result in a reduced residual capacity, causing increased structural interference when performing

two tasks simultaneously. Although we found increased brain activation, reduced upregulation from single- to dual-task, and greater DTC in old compared with young adults, we did not find any correlations between the fMRI measures and DTC. There was no dual-task specific activation in either age group. Therefore, it seems unlikely that the greater DTC in old adults were due to increased structural interference or differences in dual-task specific activation. A promising future research topic is to determine whether processing bottlenecks are present during continuous dual-tasks using high-temporal resolution measures (e.g. time-resolved fMRI).

REFERENCES

1. Lajoie Y, Teasdale N, Bard C, Fleury M. Attentional demands for static and dynamic equilibrium. Exp Brain Res 1993;97(1):139-144.

2. Riley MA, Baker AA, Schmit JM, Weaver E. Effects of visual and auditory short-term memory tasks on the spatiotemporal dynamics and variability of postural sway. J Mot Behav 2005 Jul;37(4):311-324.

3. Siu KC, Woollacott MH. Attentional demands of postural control: the ability to selectively allocate information-processing resources. Gait Posture 2007 Jan;25(1):121-126.

4. Maki BE, McIlroy WE. Influence of arousal and attention on the control of postural sway. J Vestib Res 1996 Jan-Feb;6(1):53-59.

5. Voelcker-Rehage C, Stronge AJ, Alberts JL. Age-related differences in working memory and force control under dual-task conditions. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2006 Sep-Dec;13(3-4):366-384.

6. Teasdale N, Bard C, LaRue J, Fleury M. On the cognitive penetrability of posture control. Exp Aging Res 1993 Jan-Mar;19(1):1-13.

7. Maylor EA, Wing AM. Age differences in postural stability are increased by additional cognitive demands. J Gerontol B Psychol Sci Soc Sci 1996 May;51(3):P143-54.

8. Hartley AA. Age differences in dual-task interference are localized to response-generation processes. Psychol Aging 2001 Mar;16(1):47-54.

9. Maquestiaux F, Hartley AA, Bertsch J. Can practice overcome age-related differences in the psychological refractory period effect? Psychol Aging 2004 Dec;19(4):649-667.

10. Ruffieux J, Keller M, Lauber B, Taube W. Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan. Sports Med 2015 Aug 8.

11. Granacher U, Muehlbauer T, Zahner L, Gollhofer A, Kressig RW. Comparison of traditional and recent approaches in the promotion of balance and strength in older adults. Sports Med 2011 May 1;41(5):377-400.

12. Gill DP, Gregory MA, Zou G, Liu-Ambrose T, Shigematsu R, Hachinski V, et al. The Healthy Mind, Healthy Mobility Trial: A Novel Exercise Program for Older Adults. Med Sci Sports Exerc 2015 Aug 17.

13. Silsupadol P, Shumway-Cook A, Lugade V, van Donkelaar P, Chou LS, Mayr U, et al. Effects of single-task versus dual-task training on balance performance in older adults: a double-blind, randomized controlled trial. Arch Phys Med Rehabil 2009 Mar;90(3):381-387.

14. Wollesen B, Voelcker-Rehage C, Willer J, Zech A, Mattes K. Feasibility study of dual-task-managing training to improve gait performance of older adults. Aging Clin Exp Res 2015 Aug;27(4):447-455.

15. Just MA, Carpenter PA, Keller TA, Emery L, Zajac H, Thulborn KR. Interdependence of nonoverlapping cortical systems in dual cognitive tasks. Neuroimage 2001 Aug;14(2):417-426.

16. Just MA, Keller TA, Cynkar J. A decrease in brain activation associated with driving when listening to someone speak. Brain Res 2008 Apr 18;1205:70-80.

17. Klingberg T, Roland PE. Interference between two concurrent tasks is associated with activation of overlapping fields in the cortex. Brain Res Cogn Brain Res 1997 Jul;6(1):1-8.

18. Nijboer M, Taatgen NA, Brands A, Borst JP, van Rijn H. Decision making in concurrent multitasking: do people adapt to task interference? PLoS One 2013 Nov 11;8(11):e79583.

19. Salvucci DD, Taatgen NA. Threaded cognition: an integrated theory of concurrent multitasking. Psychol Rev 2008 Jan;115(1):101-130.

20. Menant JC, Sturnieks DL, Brodie MA, Smith ST, Lord SR. Visuospatial tasks affect locomotor control more than nonspatial tasks in older people. PLoS One 2014 Oct 6;9(10):e109802.

21. Nijboer M, Borst J, van Rijn H, Taatgen N. Single-task fMRI overlap predicts concurrent multitasking interference. Neuroimage 2014 Oct 15;100:60-74.

22. Papegaaij S, Taube W, Baudry S, Otten E, Hortobagyi T. Aging causes a reorganization of cortical and spinal control of posture. Front Aging Neurosci 2014 Mar 3;6:28.

23. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. Neurosci Biobehav Rev 2010 Apr;34(5):721-733.

24. Voelcker-Rehage C, Alberts JL. Effect of motor practice on dual-task performance in older adults. J Gerontol B Psychol Sci Soc Sci 2007 May;62(3):P141-8.

25. Van Impe A, Coxon JP, Goble DJ, Wenderoth N, Swinnen SP. Age-related changes in brain activation underlying single- and dual-task performance: visuomanual drawing and mental arithmetic. Neuropsychologia 2011 Jul;49(9):2400-2409.

26. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature 1995 Nov 16;378(6554):279-281.

27. Dreher JC, Grafman J. Dissociating the roles of the rostral anterior cingulate and the lateral prefrontal cortices in performing two tasks simultaneously or successively. Cereb Cortex 2003 Apr;13(4):329-339.

28. Wu T, Liu J, Hallett M, Zheng Z, Chan P. Cerebellum and integration of neural networks in dual-task processing. Neuroimage 2013 Jan 15;65:466-475.

29. Szameitat AJ, Schubert T, Muller K, Von Cramon DY. Localization of executive functions in dual-task performance with fMRI. J Cogn Neurosci 2002 Nov 15;14(8):1184-1199.

30. Adcock RA, Constable RT, Gore JC, Goldman-Rakic PS. Functional neuroanatomy of executive processes involved in dual-task performance. Proc Natl Acad Sci U S A 2000 Mar 28;97(7):3567-3572.

31. Johannsen L, Li KZ, Chechlacz M, Bibi A, Kourtzi Z, Wing AM. Functional neuroimaging of the interference between working memory and the control of periodic ankle movement timing. Neuropsychologia 2013 Sep;51(11):2142-2153.

32. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial.

JAMA 2014 Jun 18;311(23):2387-2396.

33. Shinkai S, Watanabe S, Kumagai S, Fujiwara Y, Amano H, Yoshida H, et al. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing 2000 Sep;29(5):441-446.

34. Talley KM, Wyman JF, Gross CR, Lindquist RA, Gaugler JE. Change in Balance Confidence and Its Associations With Increasing Disability in Older Community-Dwelling Women at Risk for Falling. J Aging Health 2014 Mar 25;26(4):616-636.

35. Beauchet O, Annweiler C, Dubost V, Allali G, Kressig RW, Bridenbaugh S, et al. Stops walking when talking: a predictor of falls in older adults? Eur J Neurol 2009 Jul;16(7):786-795.

36. Walshe EA, Patterson MR, Commins S, Roche RA. Dual-task and electrophysiological markers of executive cognitive processing in older adult gait and fall-risk. Front Hum Neurosci 2015 Apr 17;9:200.

37. Wang X, Pi Y, Chen P, Liu Y, Wang R, Chan C. Cognitive motor interference for preventing falls in older adults: a systematic review and meta-analysis of randomised controlled trials. Age Ageing 2015 Mar;44(2):205-212.

38. Beauchet O, Annweiler C, Allali G, Berrut G, Herrmann FR, Dubost V. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? J Am Geriatr Soc 2008 Jul;56(7):1265-1269.

39. Karim HT, Sparto PJ, Aizenstein HJ, Furman JM, Huppert TJ, Erickson KI, et al. Functional MR imaging of a simulated balance task. Brain Res 2014 Mar 25;1555:20-27.

40. Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. Brain 1999 Feb;122 (Pt 2)(Pt 2):329-338.

41. Jahn K, Deutschlander A, Stephan T, Strupp M, Wiesmann M, Brandt T. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. Neuroimage 2004 Aug;22(4):1722-1731.

42. Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiol Aging 2012 Jun;33(6):1073-1084.

43. Taube W, Mouthon M, Leukel C, Hoogewoud HM, Annoni JM, Keller M. Brain activity during observation and motor imagery of different balance tasks: an fMRI study. Cortex 2015 Mar;64:102-114.

44. Godde B, Voelcker-Rehage C. More automation and less cognitive control of imagined walking movements in high- versus low-fit older adults. Front Aging Neurosci 2010;2:10.3389/fnagi.2010.00139.

45. Kong J, Wang C, Kwong K, Vangel M, Chua E, Gollub R. The neural substrate of arithmetic operations and procedure complexity. Brain Res Cogn Brain Res 2005 Mar;22(3):397-405.

46. Cowell SF, Egan GF, Code C, Harasty J, Watson JD. The functional neuroanatomy of simple calculation and number repetition: A parametric PET activation study. Neuroimage 2000 Nov;12(5):565-573.

47. Yi-Rong N, Si-Yun S, Zhou-Yi G, Si-Run L, Yun B, Song-Hao L, et al. Dissociated brain organization for two-digit addition and subtraction: an fMRI investigation. Brain Res Bull 2011 Nov 25;86(5-6):395-402.

48. Vansteensel MJ, Bleichner MG, Freudenburg ZV, Hermes D, Aarnoutse EJ, Leijten FS, et al. Spatiotemporal characteristics of electrocortical brain activity during mental calculation. Hum Brain Mapp 2014 Dec;35(12):5903-5920.

49. Ekdahl C, Jarnlo GB, Andersson SI. Standing balance in healthy subjects. Evaluation of a quantitative test battery on a force platform. Scand J Rehabil Med 1989;21(4):187-195.

50. Bock O. Dual-task costs while walking increase in old age for some, but not for other tasks: an experimental study of healthy young and elderly persons. J Neuroeng Rehabil 2008 Nov 13;5:27-0003-5-27.

51. Tukey JW. Exploratory Data Analysis. : Addison-Wesley; 1977.

52. Hoaglina DC, Iglewiczb B. Fine-tuning some resistant rules for outlier labeling. J Amer Statist Assoc 1987;82(400):1147-1149.

53. Feinberg DA, Moeller S, Smith SM, Auerbach E, Ramanna S, Gunther M, et al. Multiplexed echo planar imaging for sub-second whole brain FMRI and fast diffusion imaging. PLoS One 2010 Dec 20;5(12):e15710.

54. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002 Jan;15(1):273-289.

55. Szameitat AJ, Schubert T, Muller HJ. How to test for dual-task-specific effects in brain imaging studies--an evaluation of potential analysis methods. Neuroimage 2011 Feb 1;54(3):1765-1773.

56. Hof AL. The equations of motion for a standing human reveal three mechanisms for balance. J Biomech 2007;40(2):451-457.

57. Cabeza R. Cognitive neuroscience of aging: contributions of functional neuroimaging. Scand J Psychol 2001 Jul;42(3):277-286.

58. Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, et al. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 2000 Jan;12(1):174-187.

59. Park DC, McDonough IM. The Dynamic Aging Mind: Revelations From Functional Neuroimaging Research. Perspect Psychol Sci 2013 Jan;8(1):62-67.

60. Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. Brain 2003 Apr;126(Pt 4):873-888.

61. Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002 Feb 26;58(4):630-635.

62. Langan J, Peltier SJ, Bo J, Fling BW, Welsh RC, Seidler RD. Functional implications of age differences in motor system connectivity. Front Syst Neurosci 2010 Jun 7;4:17.

63. McGregor KM, Zlatar Z, Kleim E, Sudhyadhom A, Bauer A, Phan S, et al. Physical activity and neural correlates of aging: a combined TMS/fMRI study. Behav Brain Res 2011 Sep 12;222(1):158-168.

64. Hamacher D, Herold F, Wiegel P, Hamacher D, Schega L. Brain activity during walking: A systematic review. Neurosci Biobehav Rev 2015 Aug 22.

65. Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. Que PASA? The posterior-anterior shift in aging. Cereb Cortex 2008 May;18(5):1201-1209.

66. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 2002 Nov;17(3):1394-1402.

67. Fera F, Weickert TW, Goldberg TE, Tessitore A, Hariri A, Das S, et al. Neural mechanisms underlying probabilistic category learning in normal aging. J Neurosci 2005 Dec 7;25(49):11340-11348.

68. Reuter-Lorenz PA, Stanczak L, Miller A. Neural recruitment and cognitive aging: two hemispheres are better than one especially as you age. Psychological Science 1999;10:494-500.

69. Cherry BJ, Adamson M, Duclos A, Hellige JB. Aging and individual variation in interhemispheric collaboration and hemispheric asymmetry. Aging Neuropsychology and Cognition 2005;12(4):316-339.

70. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008 Jan 2;28(1):91-99.

71. Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR. Aging reduces neural specialization in ventral visual cortex. Proc Natl Acad Sci U S A 2004 Aug 31;101(35):13091-13095.

72. Riecker A, Groschel K, Ackermann H, Steinbrink C, Witte O, Kastrup A. Functional significance of age-related differences in motor activation patterns. Neuroimage 2006 Sep;32(3):1345-1354.

73. Wu T, Hallett M. Neural correlates of dual task performance in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2008 Jul;79(7):760-766.

74. Schubert T, Szameitat AJ. Functional neuroanatomy of interference in overlapping dual tasks: an fMRI study. Brain Res Cogn Brain Res 2003 Oct;17(3):733-746.

75. Herath P, Klingberg T, Young J, Amunts K, Roland P. Neural correlates of dual task interference can be dissociated from those of divided attention: an fMRI study. Cereb Cortex 2001 Sep;11(9):796-805.

76. Salo E, Rinne T, Salonen O, Alho K. Brain activations during bimodal dual tasks depend on the nature and combination of component tasks. Front Hum Neurosci 2015 Feb 26;9:102.

77. Pashler H. Dual-task interference in simple tasks: data and theory. Psychol Bull 1994 Sep;116(2):220-244.

78. Navon D, Miller J. Role of outcome conflict in dual-task interference. J Exp Psychol Hum Percept Perform 1987 Aug;13(3):435-448.

79. Stelzel C, Schubert T. Interference effects of stimulus-response modality pairings in dual tasks and their robustness. Psychol Res 2011 Nov;75(6):476-490.

80. Pashler H. Processing stages in overlapping tasks: evidence for a central bottleneck. J Exp Psychol Hum Percept Perform 1984 Jun;10(3):358-377.

81. Dux PE, Ivanoff J, Asplund CL, Marois R. Isolation of a central bottleneck of information processing with time-resolved FMRI. Neuron 2006 Dec 21;52(6):1109-1120.

82. Sigman M, Dehaene S. Parsing a cognitive task: a characterization of the mind's bottleneck. PLoS Biol 2005 Feb;3(2):e37.

83. Sosnoff JJ, Socie MJ, Sandroff BM, Balantrapu S, Suh Y, Pula JH, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. Disabil Rehabil 2014;36(3):205-209.

84. Prosperini L, Castelli L, Sellitto G, De Luca F, De Giglio L, Gurreri F, et al. Investigating the phenomenon of "cognitive-motor interference" in multiple sclerosis by means of dual-task posturography. Gait Posture 2015 Mar;41(3):780-785.

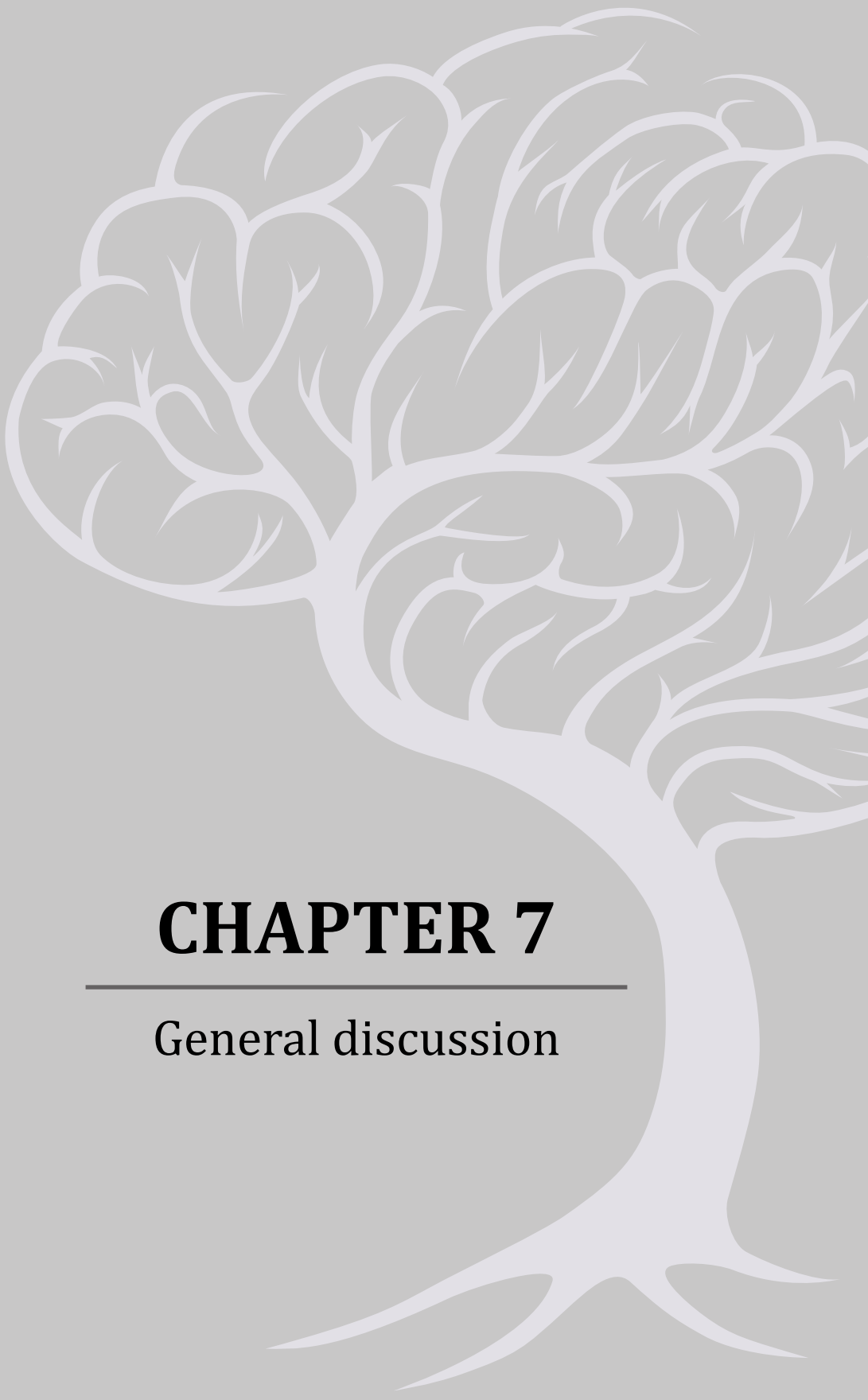
SUPPLEMENTARY MATERIAL

Brain deactivation

AAL location	Side	Dual-task				Balance				Calculation			
		MNI coordinates			t-value	MNI coordinates			t-value	MNI coordinates			t-value
		x	y	z		x	y	z		x	y	z	
Medial frontal gyrus	L	0	60	15	12.3					-3	60	15	17.1
	R	12	33	60	7.7					12	42	51	10.4
Superior frontal gyrus	L	-9	27	63	9.7	-18	57	3	4.8	-9	27	63	12.8
	R	15	60	24	5.6								
Middle frontal gyrus	L	-39	18	51	5.2					-36	18	48	7.9
Inferior frontal gyrus (orbital part)	L									-36	33	-12	5.8
	R									36	18	-21	5.5
Inferior frontal gyrus (pars triangularis)	L	-54	30	9	4.9					-54	30	9	7.1
Medial orbitofrontal cortex	L	-3	51	-6	10.7					-3	51	-6	14.0
Insula	L	-27	15	-18	6.5					-27	15	-18	6.3
	R	39	-12	18	5.6					42	-9	3	5.6
Anterior cingulate gyrus	L	0	36	3	10.7	0	33	6	7.1	0	36	0	12.9
Midcingulate area	L	0	-48	33	12.1					0	-48	33	15.8
Postcentral gyrus	L									-21	-42	75	5.3
	R									21	-42	69	8.7
Precuneus	L	-9	-54	9	5.8								
	R					9	-48	39	5.1				
Angular gyrus	L	-51	-66	36	11.0	-42	-75	39	5.8	-54	-66	30	14.4
	R	51	-66	36	10.9	48	-69	36	5.1	51	-60	24	14.0
Supramarginal gyrus	L									-63	-30	33	5.6
	R									60	-24	30	7.1
Superior temporal pole	L									-39	21	-18	6.4
	R	27	6	-24	5.6					30	9	-24	6.5
Middle temporal pole	R	48	18	-33	5.0					48	18	-33	5.7
Middle temporal gyrus	L	-63	-9	-15	8.6					-63	-9	-15	11.2
	R	66	-15	-12	5.8					60	-9	-18	8.0
Hippocampus	L	-27	-21	-18	5.8					-27	-18	-18	6.7
Parahippocampal gyrus	L	-27	-42	-9	5.7								
	R	24	-36	-12	5.4					21	-36	-12	6.0
Amygdala	L	-18	-3	-18	5.3					-18	0	-18	7.1
	R									24	-3	-18	6.4
Olfactory cortex	L									0	12	-6	10.2

Superior occipital gyrus	L									-15	-96	27	6.3
Middle occipital gyrus	L									-36	-90	21	5.7
	R									39	-84	27	7.6
Calcarine sulcus	L					-12	-57	6	5.2				
	R					9	-78	3	6.0				
Lingual gyrus	L					-9	-78	-3	5.5	-24	-45	-9	6.5
Cuneus	L	-6	-93	30	6.1	0	-87	33	10.0	-9	-90	36	4.9
	R	6	-87	33	5.8					21	-87	39	4.9
Caudate nucleus	L	-3	15	-6	7.7								
Cerebellum (lobule 9)	R									6	-51	-45	4.8
Cerebellar hemisphere (crus I)	L									-27	-81	-33	8.0
	R	27	-81	-33	7.8					24	-84	-33	8.8
Cerebellar hemisphere (crus II)	L	-30	-81	-36	6.4								

MNI coordinates and t-values of the local maxima with significant deactivation during balance, calculation and dual-tasking ($p < 0.05$; FWE corrected for multiple comparisons). Voxel size is 3x3x3 mm.



CHAPTER 7

General discussion

1. GENERAL DISCUSSION

A review of the literature reveals that old compared with young adults exhibit differential modulation of spinal reflexes, higher brain activation, and lower cortical inhibition during voluntary manual tasks, suggesting a shift from spinal to supraspinal control. Although some studies indicate that this reorganization is also present during postural tasks, evidence is limited, and functional significance of such reorganization is unknown. The aim of this thesis was therefore to determine the age-related changes in neural control of posture, as quantified by measures of motor cortical excitability and brain activation, and how such changes affect body sway during standing. We conducted a series of experiments examining the influence of age and postural task difficulty on intracortical inhibition and facilitation. Figure 1 summarizes the main outcomes of these studies, demonstrating a down-modulation in intracortical inhibition with an increase in postural task difficulty and an age by condition interaction when comparing standing on a rigid platform with standing on foam. In a final study, we further increased postural task difficulty by adding a cognitive task and examined age-related changes in neural correlates of posture and dual-tasking using functional magnetic resonance imaging (fMRI). As expected, we found increased brain activation and greater dual-task costs in old compared with young adults. However, there were no correlations between the fMRI and behavioral measures. Below, I will discuss the main findings of this thesis in more detail.

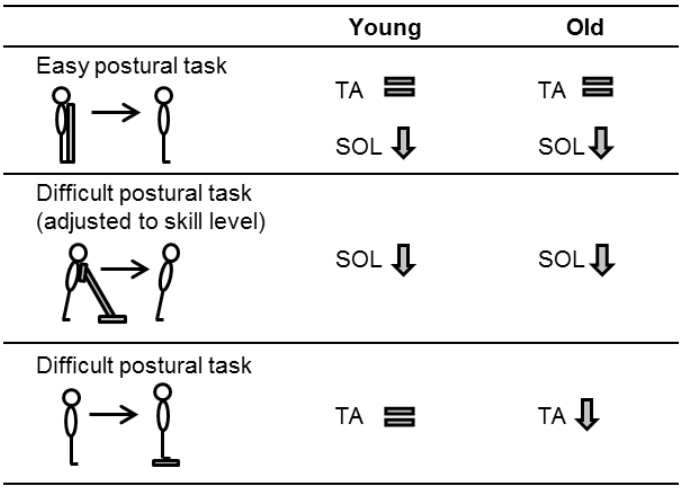


Figure 1 | Overview of modulation in measures of intracortical inhibition in young and old adults as described in chapters 3 to 5. Arrows and equality signs indicate the modulation from supported to unsupported standing (upper line) and leaning (middle line), and from standing on a rigid platform to standing on foam (lower line). Task difficulty during leaning was adjusted to skill level by setting the leaning target to 75% of the maximum per participant. TA: tibialis anterior, SOL: soleus.

1.1. Cortical control of standing

This thesis adds to the body of literature supporting the involvement of cortical structures in postural control of standing [1-6]. Performing a simulated balance task activated cortical regions such as the premotor cortex, prefrontal cortex, inferior and middle frontal gyrus, SMA, visual cortex, insula, and inferior parietal areas (chapter 6). Brain regions that were also reported to be active during mental imagery and action observation of standing using fMRI [2] or actual standing using PET-scans [4]. A new aspect that is highlighted by this thesis is the role of intracortical inhibition in postural control, which was shown to modulate with postural task difficulty (chapters 3-5). Functional significance of this modulation was further supported by correlations between the amount of modulation and behavioral measures, such as center of pressure velocity (chapter 3) and forward lean (chapter 5). In young adults, the modulation was apparent only in the soleus, which is the main muscle controlling standing posture [7]. This is consistent with the view that the down-modulation in intracortical inhibition is targeted specifically to increase the excitability of corticospinal neurons projecting to motor neurons of the muscles that are involved in the task. In old adults, however, intracortical inhibition was modulated also in the tibialis anterior when standing on foam as compared with standing on a rigid surface. This may indicate an age-related increase in involvement of the tibialis anterior to control standing on an unstable surface, i.e., on foam, supported by higher levels of tibialis anterior activity. However, changes in intracortical inhibition did not correlate with changes in background EMG. Moreover, down-modulation in intracortical inhibition also occurred when background EMG was similar between conditions (chapter 5). Reducing intracortical inhibition is therefore probably not simply a mechanism to increase descending drive. It is speculated that it represents an increased readiness state of the motor cortex to prepare for potential perturbations.

1.2. Age-related changes in cortical control of standing

Old compared with young adults generally exhibit more brain activation and lower cortical inhibition when performing a voluntary manual task (chapter 2). This thesis shows that similar age-related changes are present during postural control of standing (chapters 3, 4 & 6). Additionally, it reveals an age effect on the modulation of intracortical inhibition between certain postural tasks (chapter 3).

We examined balance-related brain activation using fMRI during a simulated standing task. In this task, old compared with young adults exhibited more activation in motor (precentral and paracentral gyri) and sensory (cuneus and precuneus) brain areas (chapter 6). Although this is consistent with Zwergal et al. [8], who reported age-related increases in brain activation during imaginary standing, we note that simulating or imagining standing is quite different from actual standing. Technical advances allowing imaging of brain activation during upright standing are

required to properly address this issue.

In chapters 3 to 5, intracortical inhibition was assessed using paired pulse and subthreshold TMS during postural tasks of varying difficulty. Age-related decreases in intracortical inhibition were found in the tibialis anterior (chapters 3 & 4) but not in the soleus (chapters 4 & 5). As is evident from figure 1, there was an age by task difficulty interaction in intracortical inhibition when young and old adults had to perform the same difficult postural task, i.e. standing on foam. As age-related sensory and motor deficits complicate postural control [9-16], standing on foam can be considered a more challenging task for old than for young adults. Therefore, the age-related difference in modulation of intracortical inhibition may have been due to the relatively higher postural challenge. This is supported by the fact that young and old adults showed similar modulation of intracortical inhibition when the postural tasks were relatively easy (normal standing) or when the difficult task was adjusted to skill level (forward leaning to 75% of your maximum) even though maximum forward lean was significantly lower in old adults. Moreover, greater reductions in intracortical inhibition were related to greater instability when standing on foam (chapter 3) and to leaning closer to the maximum during unsupported leaning (chapter 5). Together, these results imply that postural challenge is the main factor influencing intracortical inhibition and that age does not affect the motor control strategy of reducing intracortical inhibition with increasing postural challenge. However, as a similar task can be more challenging for old compared with young adults, the threshold for down-modulation decreases with aging.

1.3. Age-related changes in intracortical inhibition are muscle specific

As briefly mentioned in the previous paragraph, old compared with young adults consistently exhibited lower intracortical inhibition in the tibialis anterior (chapters 3 and 4), but similar intracortical inhibition in the soleus (chapters 4 and 5). This muscle specificity may be explained by differences in corticospinal projections, which are much stronger in the tibialis anterior than in the soleus [17-20]. Also in the upper extremity, intracortical inhibition is lower [21-23] or similar [24-27] in old compared with young adults when examined in muscles with strong corticospinal projections (hand muscles), and higher when examined in muscles with weaker corticospinal projections (wrist flexors and extensors) [28,29]. Together, these data suggest that the influence of age on intracortical inhibition is dependent on the examined muscle and its corticospinal projections.

The question arises what the underlying causes are for such muscle specificity. One reason could be that it reflects a compensatory mechanism to the varying effects of aging on different muscles [30,31]. Histochemical data indeed indicate greater age-related changes in the extensor digitorum brevis, a small hand muscle, than in more proximal arm muscles [30]. To our knowledge, there is no data available for such comparisons between the tibialis anterior and the soleus. However, muscle strength actually seems more preserved in the tibialis anterior than in the sole-

us [32,33]. Therefore, the age-related changes in intracortical inhibition do not seem to be related to the effect of age on the muscle. An alternative explanation could be that the muscle specificity is related to the different muscle functions. Monosynaptic corticospinal connections are thought to be evolved in primates to allow skilled precision control [34]. The muscle specificity may therefore reflect a mechanism of the aging nervous system to maximize corticospinal input to specific muscles favoring fine over gross motor control. In the case of the tibialis anterior this may be particularly important because of its role in toe clearance during erect walking, which requires extreme precision control [35,36] and flexibility to avoid obstacles [20,37].

1.4. No age- or task-related changes in intracortical facilitation

Besides intracortical inhibition, we also examined intracortical facilitation. Our finding of no age-related changes in intracortical facilitation (chapters 3 and 4) agrees with the majority of previous studies [25,38,39], although others reported decreased intracortical facilitation in old compared with young adults [40,41]. As our measurements were taken during standing, our finding is also consistent with McGinley et al. [42], who reported no difference in intracortical facilitation between age groups during a weak isometric muscle contraction. Our second finding was that there was no modulation between postural tasks (chapters 3 and 4). Great inconsistency exists in the literature regarding modulation of intracortical facilitation between postures, with reports of reduced [43], similar [44], and increased [45] intracortical facilitation during standing as compared with sitting. These inconsistencies may be caused by methodological differences like the examined muscle, stimulation intensity and interstimulus interval, and/or reflect the high between-subject variability of this measure. This thesis is the first to examine intracortical circuits between various task difficulty situations of standing and suggests that during standing motor cortical excitability is modulated through intracortical inhibition and not facilitation.

1.5. Age-related functional changes: deterioration or compensation?

We proposed a classification model of the different domains of age-related changes in the neuromotor system; structural, functional, and behavioral changes (chapter 2, figure 1). Functional changes were subdivided into deterioration (as a direct result of the structural changes) and compensation (changes in function to counteract the deterioration). As the subsequent chapters described several age-related functional changes, an interesting and important topic of discussion is whether these changes are due to deterioration or compensation. For example, in chapter 3 we reported that old but not young adults down-modulate intracortical inhibition when standing on foam as compared to a rigid surface. Greater down-modulation was correlated with greater increases in center of pressure velocity (i.e. worse performance). One interpretation of this finding is that increases in center of pressure velocity were caused by the down-modulation in intracortical inhibition, suggesting a functional deterioration. Alternatively, old adults with higher center of

pressure velocity had a greater need to adjust intracortical inhibition, as a compensation for the greater instability. The latter explanation was supported by chapter 5, where task difficulty was adjusted to individual skill level, and modulation of EMG suppression, presumably representing intracortical inhibition, was similar between young and old adults. Moreover, leaning closer to the maximum was correlated with greater reductions in EMG suppression; again suggesting that intracortical inhibition decreases in unstable situations. Therefore, assuming that both chapters measured similar inhibitory mechanisms, the different modulation in old adults reported in chapter 3 was most likely a compensatory mechanism.

Another age-related functional change reported in this thesis (chapter 6) and previous studies [8,46-53] is an age-related increase in brain activation during motor and cognitive tasks. Although this finding is consistent among studies, there is no consensus yet on its functional meaning. Both positive [49,54-58] and negative [48,50,53,59] correlations with behavioral performance have been reported, suggesting that the functional meaning may be dependent on the task and the involved brain structures. We found no correlations between brain activation in the "over-activated" areas and performance on a calculation and visuomotor balance simulation task. Van Impe et al. [60] used comparable tasks (calculation and visuomotor drawing), reported similar brain areas with higher activation in old adults (precentral gyrus, paracentral lobule, precuneus), and also no correlation with performance. Therefore, it seems that at least in such tasks a functional deterioration occurs with an age-related spreading of brain activity without functional meaning.

1.6. Motor cortical control is similar for postural and non-postural contractions

Voluntary and postural contractions are often considered distinct entities even though little is known about the underlying neural mechanisms. Neural control of voluntary and postural contractions has been investigated by comparing muscle contractions during sitting or lying with standing [43,61-65]. An important limitation of these studies is that conditions did not only differ in the aim of the contraction (postural or non-postural), but also in posture (sitting or lying vs. standing) and postural challenge. In chapter 5 we aimed to dissociate how these different factors affect TMS-induced EMG suppression by comparing sitting, supported leaning, and unsupported leaning. EMG suppression decreased during unsupported leaning, probably reflecting a reduction in intracortical inhibition. There was no difference in EMG suppression between sitting and supported leaning. We concluded that postural challenge, which was high during unsupported leaning and low during sitting and supported leaning, was the main factor affecting intracortical inhibition. The aim of the contraction, postural or non-postural, did not seem to influence intracortical inhibition. This supports the idea that, as long as postural challenge is unchanged, there is no difference in neural control of postural and non-postural contractions. This idea is further supported by the fact that the age-related changes in motor cortical control of posture described

in chapters 3 to 6, i.e. reduced intracortical inhibition and increased cortical activation, were similar to those previously reported in voluntary manual tasks (chapter 2). However, other inhibitory and excitatory circuits within the brain that we did not measure may still be involved differently in postural and non-postural contractions.

1.7. Neural correlates of dual-tasking

In addition to changing sensory input or support, postural task difficulty can also be modified by adding a cognitive task. Especially old adults generally have difficulty with performing two tasks simultaneously and show greater dual-task costs than young adults [66-68]. We hypothesized that this age-related deficit in dual-task performance may be related to the increased cortical activation when performing a motor or cognitive task (chapter 2). In chapter 6, this was tested using fMRI during a simulated balance task combined with a mental arithmetic task. Although age-related increases in brain activation and dual-task costs were found, there were no correlations between the behavioral and fMRI measures, contradicting our hypothesis. It therefore seems that, at least in these tasks, the increased brain activation did not affect dual-tasking. It remains to be explored what did cause the reduced dual-tasking performance in old adults. One alternative theory is that there is a central bottleneck that can perform certain processes only sequentially, resulting in serial queuing and time delays [69]. Future research using high-temporal resolution measures such as time-resolved fMRI [70] will test this hypothesis.

1.8. Limitations and future recommendations

This thesis has several limitations. First, the currently available measures for intracortical inhibition are not perfect. Although there is quite convincing evidence that the subthreshold TMS pulse stimulates intracortical inhibitory neurons [71-73]; background EMG [43,74,75], stimulation intensity [76], cortical facilitatory circuits, and the extent of cortical involvement in the ongoing EMG [77] can also affect the outcome. Second, as motor threshold and stimulation hotspot slightly differ between the soleus and tibialis anterior, it is difficult to acquire reliable data from both muscles in one experiment. Therefore, in our first study comparing easy and difficult postural tasks, we focused on the tibialis anterior. Future research is needed to ascertain that the age by task difficulty interaction in intracortical inhibition also occurs when examining the soleus muscle. A third limitation is that the simulated balance task in chapter 6 differs from actual balance in several ways, e.g., different sensory input from the vestibular system, no real threat of falling, and no weight-bearing. Although torque variability during a plantar flexion torque-matching task correlated with torque variability during actual standing [78,79] and the simulated balance task activated brain regions supposed to be involved in balance (chapter 6), caution is still required with regard to the external validity of the task. Technical advances are needed to provide means to properly examine neural correlates of standing in the future.

1.9. Clinical implications

A better understanding of the age-related differences in neural control of posture is essential for the development of fall prevention and intervention programs for old adults. This thesis provides evidence that the ability to adjust motor cortical excitability to different environments is unaffected by age (chapters 4 and 5). Balance training should therefore focus on other aspects of postural control, such as sensory input [80] and muscle power [12,81]. This thesis also confirms previous reports that old compared with young adults have more difficulty with performing a cognitive and balance task simultaneously [66-68] (chapter 6). Another important aspect of balance training in old adults should thus be to practice such dual-task situations [12]. Lastly, as age-related differences in neural measures were found only during difficult balance tasks (chapter 3), this thesis underpins that including relatively difficult balance exercises may be essential in order to cause neural adaptations [82]. Future work is needed to verify this suggestion and examine changes in motor cortical excitability that are induced by balance training in old adults.

1.10. Conclusions

The aim of this thesis was to determine the age-related changes in neural control of posture, as quantified by measures of motor cortical excitability and brain activation, and how such changes affect body sway during standing. The results show an age-related muscle-specific reduction in intracortical inhibition and increase in cortical activation during postural tasks, suggesting a similar neural reorganization with age as during manual tasks. Age-related increases in brain activation did not correlate with single- or dual-task performance, favoring the theory of de-differentiation over compensation. Modulation of intracortical inhibition between postural tasks differed between age groups when comparing an easy with a difficult task, but was similar when adjusting task difficulty to the individual skill level. This implies that the ability to modulate intracortical inhibition by postural challenge is unaffected by age, but the threshold for down-modulation is lower in old as compared with young adults. Functional significance of the task-related modulation in intracortical inhibition was supported by correlations with behavioral measures.

REFERENCES

1. Jacobs JV, Horak FB. Cortical control of postural responses. J Neural Transm 2007;114(10):1339-1348.

2. Taube W, Mouthon M, Leukel C, Hoogewoud HM, Annoni JM, Keller M. Brain activity during observation and motor imagery of different balance tasks: an fMRI study. Cortex 2015 Mar;64:102-114.

3. Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A. Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. J Appl Physiol 2006 Aug;101(2):420-429.

4. Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. Brain 1999 Feb;122 (Pt 2)(Pt 2):329-338.

5. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of

human standing. Acta Physiol (Oxf) 2009 Mar;195(3):385-395.

6. Hulsdunker T, Mierau A, Neeb C, Kleinoder H, Struder HK. Cortical processes associated with continuous balance control as revealed by EEG spectral power. Neurosci Lett 2015 Apr 10;592:1-5.

7. Di Giulio I, Maganaris CN, Baltzopoulos V, Loram ID. The proprioceptive and agonist roles of gastrocnemius, soleus and tibialis anterior muscles in maintaining human upright posture. J Physiol 2009 May 15;587(Pt 10):2399-2416.

8. Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiol Aging 2012 Jun;33(6):1073-1084.

9. McChesney JW, Woollacott MH. The effect of age-related declines in proprioception and total knee replacement on postural control. J Gerontol A Biol Sci Med Sci 2000 Nov;55(11):M658-66.

10. Aartolahti E, Hakkinen A, Lonnroos E, Kautiainen H, Sulkava R, Hartikainen S. Relationship between functional vision and balance and mobility performance in community-dwelling older adults. Aging Clin Exp Res 2013 Oct;25(5):545-552.

11. Lord SR. Visual risk factors for falls in older people. Age Ageing 2006 Sep;35 Suppl 2:ii42-ii45.

12. Granacher U, Muehlbauer T, Zahner L, Gollhofer A, Kressig RW. Comparison of traditional and recent approaches in the promotion of balance and strength in older adults. Sports Med 2011 May 1;41(5):377-400.

13. Orr R, Raymond J, Fiatarone Singh M. Efficacy of progressive resistance training on balance performance in older adults : a systematic review of randomized controlled trials. Sports Med 2008;38(4):317-343.

14. Perry MC, Carville SF, Smith IC, Rutherford OM, Newham DJ. Strength, power output and symmetry of leg muscles: effect of age and history of falling. Eur J Appl Physiol 2007 Jul;100(5):553-561.

15. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2004 Jul;52(7):1121-1129.

16. Serrador JM, Lipsitz LA, Gopalakrishnan GS, Black FO, Wood SJ. Loss of otolith function with age is associated with increased postural sway measures. Neurosci Lett 2009 Nov 6;465(1):10-15.

17. Brouwer B, Ashby P. Corticospinal projections to lower limb motoneurons in man. Exp Brain Res 1992;89(3):649-654.

18. Nielsen J, Petersen N, Deuschl G, Ballegaard M. Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man. J Physiol 1993 Nov;471:223-243.

19. Bawa P, Chalmers GR, Stewart H, Eisen AA. Responses of ankle extensor and flexor motoneurons to transcranial magnetic stimulation. J Neurophysiol 2002 Jul;88(1):124-132.

20. Trinastic JP, Kautz SA, McGregor K, Gregory C, Bowden M, Benjamin MB, et al. An fMRI study of the differences in brain activity during active ankle dorsiflexion and plantarflexion. Brain Imaging Behav 2010 Jun;4(2):121-131.

21. Opie GM, Semmler JG. Age-related differences in short- and long-interval intracortical inhibition in a human hand muscle. Brain Stimul 2014 Sep-Oct;7(5):665-672.

22. Heise KF, Zimerman M, Hoppe J, Gerloff C, Wegscheider K, Hummel FC. The Aging Motor System as a Model for Plastic Changes of GABA-Mediated Intracortical Inhibition and Their Behavioral Relevance. J Neurosci 2013 May 22;33(21):9039-9049.

23. Marneweck M, Loftus A, Hammond G. Short-interval intracortical inhibition and manual dexterity in

healthy aging. Neurosci Res 2011 Aug;70(4):408-414.

24. Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, et al. Effects of aging on motor cortex excitability. Neurosci Res 2006 May;55(1):74-77.

25. Smith AE, Ridding MC, Higgins RD, Wittert GA, Pitcher JB. Cutaneous afferent input does not modulate motor intracortical inhibition in ageing men. Eur J Neurosci 2011 Nov;34(9):1461-1469.

26. Rogasch NC, Dartnall TJ, Cirillo J, Nordstrom MA, Semmler JG. Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. J Appl Physiol 2009 Dec;107(6):1874-1883.

27. Cirillo J, Todd G, Semmler JG. Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. Eur J Neurosci 2011 Dec;34(11):1847-1856.

28. Brouwer B, Ashby P. Corticospinal projections to upper and lower limb spinal motoneurons in man. Electroencephalogr Clin Neurophysiol 1990 Dec;76(6):509-519.

29. de Noordhout AM, Rapisarda G, Bogacz D, Gerard P, De Pasqua V, Pennisi G, et al. Corticomotoneuronal synaptic connections in normal man: an electrophysiological study. Brain 1999 Jul;122 (Pt 7)(Pt 7):1327-1340.

30. Jennekens FG, Tomlinson BE, Walton JN. Histochemical aspects of five limb muscles in old age. An autopsy study. J Neurol Sci 1971 Nov;14(3):259-276.

31. Kirkeby S, Garbarsch C. Aging affects different human muscles in various ways. An image analysis of the histomorphometric characteristics of fiber types in human masseter and vastus lateralis muscles from young adults and the very old. Histol Histopathol 2000 Jan;15(1):61-71.

32. Winegard KJ, Hicks AL, Sale DG, Vandervoort AA. A 12-year follow-up study of ankle muscle function in older adults. J Gerontol A Biol Sci Med Sci 1996 May;51(3):B202-7.

33. Danneskiold-Samsoe B, Bartels EM, Bulow PM, Lund H, Stockmarr A, Holm CC, et al. Isokinetic and isometric muscle strength in a healthy population with special reference to age and gender. Acta Physiol (Oxf) 2009 Oct;197 Suppl 673:1-68.

34. Lemon RN. Descending pathways in motor control. Annu Rev Neurosci 2008;31:195-218.

35. Winter DA, Bishop PJ. Lower extremity injury. Biomechanical factors associated with chronic injury to the lower extremity. Sports Med 1992 Sep;14(3):149-156.

36. Petersen NT, Pyndt HS, Nielsen JB. Investigating human motor control by transcranial magnetic stimulation. Exp Brain Res 2003 Sep;152(1):1-16.

37. Loverro KL, Mueske NM, Hamel KA. Location of minimum foot clearance on the shoe and with respect to the obstacle changes with locomotor task. J Biomech 2013 Jul 26;46(11):1842-1850.

38. Smith AE, Ridding MC, Higgins RD, Wittert GA, Pitcher JB. Age-related changes in short-latency motor cortex inhibition. Exp Brain Res 2009 Oct;198(4):489-500.

39. Stevens-Lapsley JE, Thomas AC, Hedgecock JB, Kluger BM. Corticospinal and intracortical excitability of the quadriceps in active older and younger healthy adults. Arch Gerontol Geriatr 2013 Jan-Feb;56(1):279-284.

40. Kossev AR, Schrader C, Dauper J, Dengler R, Rollnik JD. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. Neurosci Lett 2002 Nov 22;333(2):83-86.

41. Bashir S, Perez JM, Horvath JC, Pena-Gomez C, Vernet M, Capia A, et al. Differential effects of motor cortical excitability and plasticity in young and old individuals: a Transcranial Magnetic Stimulation (TMS) study.

Front Aging Neurosci 2014 Jun 10;6:111.

42. McGinley M, Hoffman RL, Russ DW, Thomas JS, Clark BC. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. Exp Gerontol 2010 Sep;45(9):671-678.

43. Soto O, Valls-Sole J, Shanahan P, Rothwell J. Reduction of intracortical inhibition in soleus muscle during postural activity. J Neurophysiol 2006 Oct;96(4):1711-1717.

44. Kantak SS, Wittenberg GF, Liao WW, Magder LS, Rogers MW, Waller SM. Posture-related modulations in motor cortical excitability of the proximal and distal arm muscles. Neurosci Lett 2013 Jan 15;533:65-70.

45. Obata H, Sekiguchi H, Ohtsuki T, Nakazawa K. Posture-related modulation of cortical excitability in the tibialis anterior muscle in humans. Brain Res 2014 Aug 19;1577:29-35.

46. Cabeza R. Cognitive neuroscience of aging: contributions of functional neuroimaging. Scand J Psychol 2001 Jul;42(3):277-286.

47. Hamacher D, Herold F, Wiegel P, Hamacher D, Schega L. Brain activity during walking: A systematic review. Neurosci Biobehav Rev 2015 Aug 22.

48. Langan J, Peltier SJ, Bo J, Fling BW, Welsh RC, Seidler RD. Functional implications of age differences in motor system connectivity. Front Syst Neurosci 2010 Jun 7;4:17.

49. Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002 Feb 26;58(4):630-635.

50. McGregor KM, Zlatar Z, Kleim E, Sudhyadhom A, Bauer A, Phan S, et al. Physical activity and neural correlates of aging: a combined TMS/fMRI study. Behav Brain Res 2011 Sep 12;222(1):158-168.

51. Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, et al. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 2000 Jan;12(1):174-187.

52. Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. Brain 2003 Apr;126(Pt 4):873-888.

53. Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR. Aging reduces neural specialization in ventral visual cortex. Proc Natl Acad Sci U S A 2004 Aug 31;101(35):13091-13095.

54. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 2002 Nov;17(3):1394-1402.

55. Cherry BJ, Adamson M, Duclos A, Hellige JB. Aging and individual variation in interhemispheric collaboration and hemispheric asymmetry. Aging Neuropsychology and Cognition 2005;12(4):316-339.

56. Fera F, Weickert TW, Goldberg TE, Tessitore A, Hariri A, Das S, et al. Neural mechanisms underlying probabilistic category learning in normal aging. J Neurosci 2005 Dec 7;25(49):11340-11348.

57. Reuter-Lorenz PA, Stanczak L, Miller A. Neural recruitment and cognitive aging: two hemispheres are better than one especially as you age. Psychological Science 1999;10:494-500.

58. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008 Jan 2;28(1):91-99.

59. Riecker A, Groschel K, Ackermann H, Steinbrink C, Witte O, Kastrup A. Functional significance of age-related differences in motor activation patterns. Neuroimage 2006 Sep;32(3):1345-1354.

60. Van Impe A, Coxon JP, Goble DJ, Wenderoth N, Swinnen SP. Age-related changes in brain activation underlying single- and dual-task performance: visuomanual drawing and mental arithmetic. Neuropsychologia 2011 Jul;49(9):2400-2409.

61. Ackermann H, Scholz E, Koehler W, Dichgans J. Influence of posture and voluntary background contraction upon compound muscle action potentials from anterior tibial and soleus muscle following transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991 Feb;81(1):71-80.

62. Lavoie BA, Cody FW, Capaday C. Cortical control of human soleus muscle during volitional and postural activities studied using focal magnetic stimulation. Exp Brain Res 1995;103(1):97-107.

63. Nakazawa K, Kawashima N, Obata H, Yamanaka K, Nozaki D, Akai M. Facilitation of both stretch reflex and corticospinal pathways of the tibialis anterior muscle during standing in humans. Neurosci Lett 2003 Feb 20;338(1):53-56.

64. Obata H, Sekiguchi H, Nakazawa K, Ohtsuki T. Enhanced excitability of the corticospinal pathway of the ankle extensor and flexor muscles during standing in humans. Exp Brain Res 2009 Aug;197(3):207-213.

65. Guzman-Lopez J, Selvi A, Sola-Valls N, Casanova-Molla J, Valls-Sole J. Effects of postural and voluntary muscle contraction on modulation of the soleus H reflex by transcranial magnetic stimulation. Exp Brain Res 2015 Dec;233(12):3425-3431.

66. Maylor EA, Wing AM. Age differences in postural stability are increased by additional cognitive demands. J Gerontol B Psychol Sci Soc Sci 1996 May;51(3):P143-54.

67. Ruffieux J, Keller M, Lauber B, Taube W. Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan. Sports Med 2015 Aug 8.

68. Bernard-Demanze L, Dumitrescu M, Jimeno P, Borel L, Lacour M. Age-related changes in posture control are differentially affected by postural and cognitive task complexity. Curr Aging Sci 2009 Jul;2(2):139-149.

69. Pashler H. Processing stages in overlapping tasks: evidence for a central bottleneck. J Exp Psychol Hum Percept Perform 1984 Jun;10(3):358-377.

70. Dux PE, Ivanoff J, Asplund CL, Marois R. Isolation of a central bottleneck of information processing with time-resolved FMRI. Neuron 2006 Dec 21;52(6):1109-1120.

71. Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, et al. Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. Clin Neurophysiol 2000 May;111(5):794-799.

72. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res 1998 Mar;119(2):265-268.

73. Davey NJ, Romaiguere P, Maskill DW, Ellaway PH. Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. J Physiol 1994 Jun 1;477 (Pt 2)(Pt 2):223-235.

74. Lackmy A, Marchand-Pauvert V. The estimation of short intra-cortical inhibition depends on the proportion of spinal motoneurones activated by corticospinal inputs. Clin Neurophysiol 2010 Apr;121(4):612-621.

75. Zoghi M, Pearce SL, Nordstrom MA. Differential modulation of intracortical inhibition in human motor cortex during selective activation of an intrinsic hand muscle. J Physiol 2003 Aug 1;550(Pt 3):933-946.

76. Garry MI, Thomson RH. The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. Exp Brain Res 2009 Feb;193(2):267-274.

77. Seifert T, Petersen NC. Changes in presumed motor cortical activity during fatiguing muscle contraction in humans. Acta Physiol (Oxf) 2010 Jul 1;199(3):317-326.

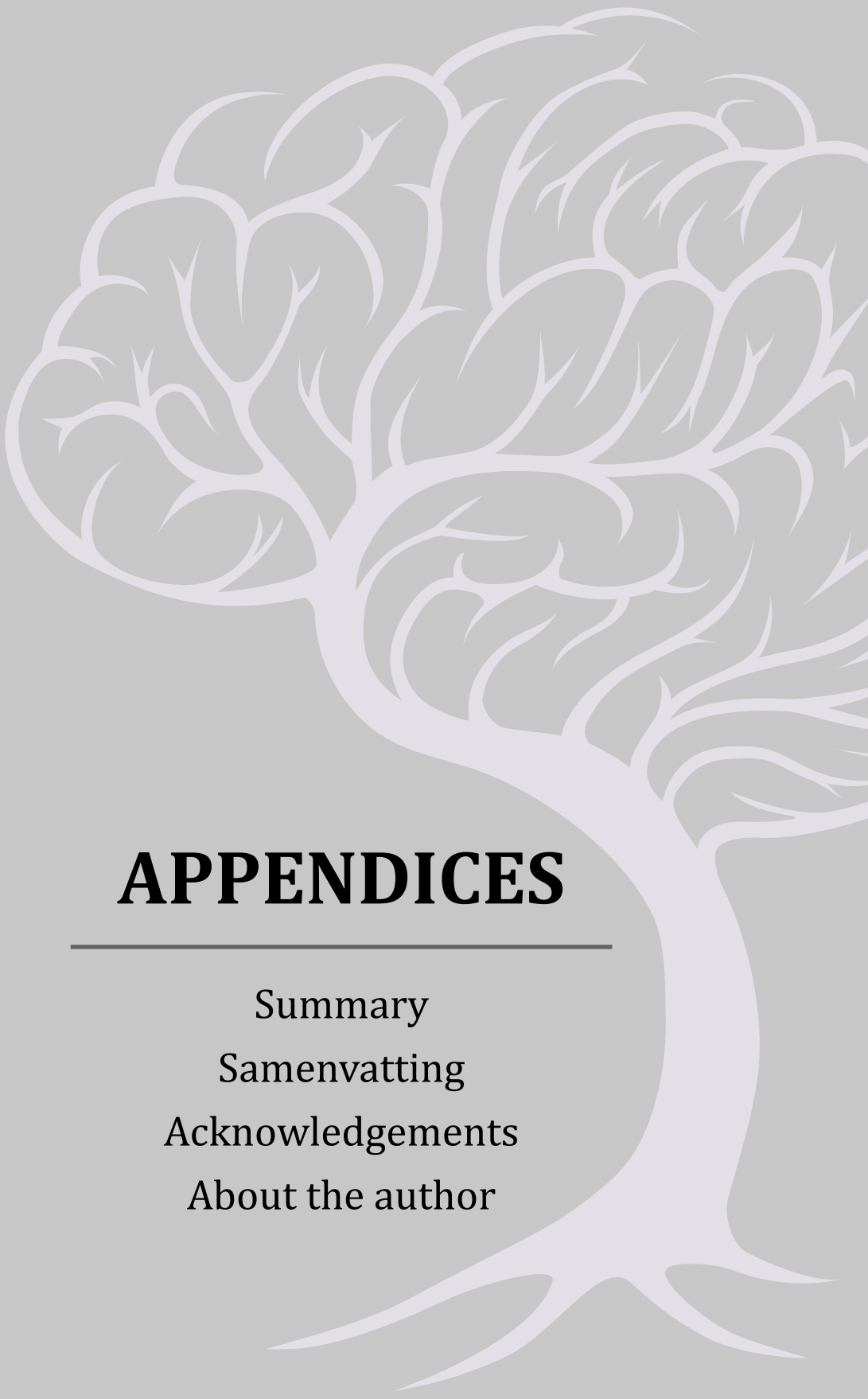
78. Kouzaki M, Shinohara M. Steadiness in plantar flexor muscles and its relation to postural sway in young and elderly adults. Muscle Nerve 2010 Jul;42(1):78-87.

79. Mello EM, Magalhaes FH, Kohn AF. Larger plantar flexion torque variability implies less stable balance in the young: An association affected by knee position. Hum Mov Sci 2013 Sep 20.

80. Aman JE, Elangovan N, Yeh IL, Konczak J. The effectiveness of proprioceptive training for improving motor function: a systematic review. Front Hum Neurosci 2015 Jan 28;8:1075.

81. Granacher U, Gollhofer A, Hortobagyi T, Kressig RW, Muehlbauer T. The importance of trunk muscle strength for balance, functional performance, and fall prevention in seniors: a systematic review. Sports Med 2013 Jul;43(7):627-641.

82. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc 2008 Dec;56(12):2234-2243.



APPENDICES

Summary

Samenvatting

Acknowledgements

About the author

SUMMARY

Natural aging is associated with adverse changes in various structures and functions, such as declines in muscle strength, sensory acuity, cognitive abilities, nerve conduction velocity, and gray and white matter. It is therefore not surprising that postural control, in this thesis defined as the control of upright standing, is compromised in old compared with young adults. Although the effects of motor and sensory decline on postural control have been studied extensively, age-related changes in neural control of posture are largely unknown. The aim of this thesis was therefore to determine the age-related changes in neural control of posture, as quantified by measures of motor cortical excitability and brain activation, and how such changes affect body sway during standing.

Classical studies in animal preparations suggest a strong role for spinal control of upright standing. In humans there is now ample evidence that the cerebral cortex also contributes to postural control. Therefore, the age-related degeneration and accompanying functional changes in the brain, reported so far mainly in conjunction with manual motor tasks, may also affect the mechanisms that control posture (chapter 2). To test this hypothesis, we performed a series of experiments using transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) designed to systematically investigate modulation of cortical activity with postural task difficulty in young and old adults.

In chapter 3, we investigated short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in the tibialis anterior during standing on a rigid platform or foam, with the eyes open or closed. There was an overall age-related decrease in SICI. Old but not young adults reduced SICI even further when standing on foam as compared with standing on a rigid platform. This reduction was associated with increases in center of pressure velocity. Age and sensory conditions did not affect ICF.

The age by task difficulty interaction in SICI did not occur in easier standing tasks, i.e. normal and supported standing (chapter 4). In the soleus, SICI was lower in normal vs. supported standing but similar in young vs. old adults. In the tibialis anterior, SICI was similar between conditions but lower in old vs. young adults. These results suggest that age only affects modulation of SICI during difficult postural tasks and that the age-related reduction in SICI is muscle-dependent.

In chapter 5, we examined whether young and old adults also modulate intracortical inhibition differently when postural task difficulty is adjusted to individual skill level. Subjects were asked to lean forward to 75% of their maximum. Intracortical inhibition during leaning, as quantified by subthreshold TMS induced suppression in the ongoing soleus EMG, was compared with that during supported leaning and sitting. The area of EMG suppression was ~60% smaller in unsupported vs. supported leaning and sitting, with no difference between these latter two conditions. Even though in absolute terms young compared with old adults leaned farther, there

was no age effect or an age by condition interaction in EMG suppression. Leaning closer to the maximum without support correlated with less EMG suppression. We concluded that age did not affect the motor control strategy as quantified by the modulation of intracortical inhibition, but the modulation appeared at a lower task difficulty with increasing age.

In chapter 6, we further increased postural task difficulty by adding a cognitive task and examined age-related changes in neural correlates of posture and dual-tasking using fMRI. Subjects performed a calculation (serial subtraction by seven) and balance-simulation (plantar flexion force control) task separately or simultaneously. As expected, old compared with young adults exhibited more brain activation during all conditions and greater dual-task costs. However, there were no correlations between the fMRI and behavioral measures. It therefore seems that, at least in these tasks, the increased brain activation did not affect dual-tasking.

Chapter 7 summarizes and discusses the main results presented in this thesis. These results show an age-related muscle-specific reduction in intracortical inhibition and increase in cortical activation during postural tasks, suggesting a similar neural reorganization with age as during manual tasks. Age-related increases in brain activation did not correlate with single- or dual-task performance, favoring the theory of de-differentiation over compensation. Modulation of intracortical inhibition between postural tasks differed between age groups when comparing an easy with a difficult task, but was similar when adjusting task difficulty to the individual skill level. This implies that the ability to modulate intracortical inhibition by postural challenge is unaffected by age, but the threshold for down-modulation is lower in old as compared with young adults. Functional significance of the task-related modulation in intracortical inhibition was supported by correlations with behavioral measures.

SAMENVATTING

Ouder worden gaat gepaard met nadelige veranderingen in verschillende structuren en functies, zoals achteruitgangen in spierkracht, sensoriek, cognitie, snelheid van zenuwgeleiding, en grijze en witte stof. Het is daarom niet verassend dat houdingscontrole, in dit proefschrift gedefinieerd als het controleren van rechtop staan, is aangetast in ouderen. Hoewel de effecten van motorische en sensorische achteruitgang op houdingscontrole uitgebreid onderzocht zijn, zijn leeftijdsgerelateerde veranderingen in het neurale aspect van houdingscontrole nog grotendeels onbekend. Het doel van dit proefschrift was daarom het bepalen van de leeftijdsgerelateerde veranderingen in neurale houdingscontrole, gekwantificeerd door metingen van de motor corticale exciteerbaarheid, en hoe zulke veranderingen de stabiliteit van het staan beïnvloeden.

Klassieke experimenten in dieren suggereren een belangrijke rol voor spinale controle van staan, maar in mensen komt er steeds meer bewijs dat de cerebrale cortex ook een bijdrage levert aan houdingscontrole. Vandaar dat de leeftijdsgerelateerde degeneratie en bijkomende functionele veranderingen in de hersenen, tot nu toe voornamelijk beschreven bij manuele motorische taken, mogelijk ook de houdingscontrole mechanismen beïnvloeden. Om deze hypothese te testen voerden we een serie TMS (transcranial magnetic stimulation) en fMRI (functional magnetic resonance imaging) experimenten uit, ontworpen om systematisch de modulatie van corticale activiteit met de moeilijkheidsgraad van de balanstaak te onderzoeken in jongeren en ouderen.

In hoofdstuk 3 onderzochten we SICI (short-interval intracortical inhibition) en ICF (intracortical facilitation) in de tibialis anterior tijdens staan op een stabiele onderdergrond of foam, met de ogen open of dicht. SICI was gemiddeld gezien lager in ouderen dan in jongeren. Bovendien verlaagden de ouderen, maar niet de jongeren, SICI nog verder tijdens het staan op foam in vergelijking met het staan op een stabiele ondergrond. Een sterkere verlaging in SICI tussen condities was geassocieerd met een sterkere verhoging in center of pressure snelheid. Er was geen invloed van leeftijd of condities op ICF.

De interactie tussen leeftijd en balans conditie in SICI vond niet plaats tijdens simpele balans taken, i.e. normaal en gesteund staan (hoofdstuk 4). In de soleus was SICI lager tijdens normaal vs. gesteund staan, maar gelijk in jongeren en ouderen. In de tibialis anterior was SICI gelijk tussen condities, maar lager in ouderen vs. jongeren. Deze resultaten suggereren dat de modulatie van SICI alleen tijdens moeilijke balanstaken beïnvloed wordt door leeftijd en dat de algemene leeftijdsgerelateerde verlaging in SICI afhankelijk is van de gemeten spier.

In hoofdstuk 5 onderzochten we of jongeren en ouderen hun intracorticale inhibitie ook anders moduleren wanneer de moeilijkheidsgraad van de balanstaak is aangepast aan de individu. Proefpersonen werden gevraagd om naar voren te leunen tot 75% van hun maximum. Intracorticale inhibitie tijdens leunen, gekwantificeerd door de suppressie in soleus EMG geïnduceerd

door subthreshold TMS, werd vergeleken met die tijdens gesteund leunen en zitten. De EMG suppressie was ~60% kleiner in ongesteund vs. gesteund leunen en zitten, met geen verschil tussen de laatste twee condities. Hoewel absoluut gezien jongeren verder leunden dan ouderen, was er geen effect van leeftijd of leeftijd met conditie interactie in EMG suppressie. Dichterbij het maximum leunen in de ongesteunde conditie correleerde met minder EMG suppressie. We concludeerden dat er geen invloed was van leeftijd op de motorische controle strategie gemeten door de modulatie van intracorticale inhibitie, maar dat de modulatie in ouderen bij een lagere absolute moeilijkheidsgraad plaatsvindt.

In hoofdstuk 6 verhoogden we de moeilijkheidsgraad verder door het toevoegen van een cognitieve taak en onderzochten we de leeftijdsgerelateerde veranderingen in neurale correlaten van houdingscontrole en dubbeltaken. Proefpersonen voerden een rekentaak (aftrekken van zeven) en een balans simulatie taak (plantairflexie kracht controle) afzonderlijk of gelijktijdig uit. Zoals verwacht lieten de ouderen tijdens alle condities meer hersenactivatie zien dan jongeren en waren ze slechter in de dubbeltaken. Daarentegen waren er geen correlaties tussen de fMRI en prestatie maten. Het lijkt er daarom op dat, tenminste tijdens deze taken, de verhoogde hersenactivatie geen invloed had op het uitvoeren van de dubbeltaak.

De belangrijkste resultaten van dit proefschrift worden samengevat en bediscussieerd in hoofdstuk 7. Deze resultaten duiden op een leeftijdsgerelateerde en spier-afhankelijke verlaging in intracorticale inhibitie en een verhoogde corticale activatie tijdens balanstaken, wat suggereert dat er een vergelijkbare neurale reorganisatie plaatsvindt met veroudering als tijdens manuele taken. Leeftijdsgerelateerde verhogingen in hersenactivatie correleerden niet met single- of dubbel-taak prestaties. Dit is in overeenstemming met de dedifferentiatie en niet met de compensatie theorie. Modulatie van intracorticale inhibitie tussen balanstaken verschilden tussen de leeftijdsgroepen wanneer een moeilijke met een makkelijke taak vergeleken werd, maar was gelijk wanneer de moeilijkheidsgraad aangepast werd aan de individu. Dit impliceert dat het vermogen om intracorticale inhibitie aan te passen aan de houdingstaak niet wordt aangetast door leeftijd, maar dat de drempel voor modulatie lager ligt in ouderen dan in jongeren.

ACKNOWLEDGEMENTS

This thesis would not be here without the extraordinary amount of help and support I had from many people. I am indebted to all who contributed to the completion of my studies directly or indirectly, also those whom I do not mention personally.

Prof. dr. T. Hortobágyi, dear Tibor, I was so lucky to have you as promotor and supervisor. I'm afraid I'm spoiled for the rest of my life expecting my future superiors to provide feedback as insanely fast and thorough as you always did. Your involvement with your students and their projects is unprecedented. You were always there for me and taught me so much over the years. I will never forget to keep looking for the bigger picture… Tibor, I thank you for your trust, your time, your support, and your endless energy. I sincerely hope and think that our collaboration does not end here.

Prof. dr. E. Otten, dear Bert, you were involved in this project as a second promotor. It was good to have someone who knew me, to whom I could go to when I needed a second opinion. Not only content wise, but also about project management and personal development in a broader perspective. Thank you very much for your support.

Prof. dr. W. Taube, dear Wolfgang, even though my German hasn't improved that much I feel like we speak the same language. I always enjoyed getting feedback from you, because I knew it would improve the manuscript tremendously. It is amazing how you can look at a manuscript and see the general line of thoughts, yet not forgetting important details. I am very grateful for your help and support.

Prof. dr. C. Voelcker-Rehage, dear Claudia, thank you so much for the opportunity to come to Germany for part of my project. It was a great experience that would not have been possible without your astonishing organization skills. You made me feel welcome and worked hard to do everything within your powers to let the project succeed.

I would also like to thank the rest of my co-authors: dr. S. Baudry, prof. dr. B. Godde, and dr. H.G. van Keeken. Their helpful comments have not only improved my writing but also my understanding of the matter. Special thanks go to Helco, for helping me setting up the laboratory and the virtual environments.

Also the technical staff has been essential for my project. Emyl Smid, Wim A. Kaan, dr. P. Erhard, Dirk van der Meer, and Dirk Schulte am Hülse, helped with the setup of many experiments and

with troubleshooting when equipment was not working. Especially chapter 6 was technically challenging and Wim and dr. P. Erhard spent many hours on writing the software and putting the hardware together. Wim and Peter, I am sorry for pushing you too much sometimes, but I am so happy and impressed you made it work.

Also I am grateful to Fraunhofer MEVIS for our collaboration and technical support, with special thanks to Jochen Hirsch for the organization.

Prof. dr. U. Granacher, dear Urs, thank you for reading and commenting on some of the chapters. Your feedback was very helpful.

Members of the reading committee, prof. dr. T. van Laar, prof. dr. N. Wenderoth, and prof. dr. J.H. van Dieën, thank you very much for your time and effort to read and review this thesis.

Over the years I had help from many students for subject recruitment and data collection. It was not only very useful but also a lot of fun, which was quite remarkable since we spent most of our summer days being locked up in the lighttight hot room that is also called the CAREN lab. Margot, Jeroen, Amelie, János, Anke, Henric-Jan, Jolien, Janine, Carolin, Nienke, and Nézar, you were great!

Of course none of the experiments would have been possible without the participants. I am most grateful for their time, patience, endurance, braveness, and trust, despite the fact I was stimulating their brain…

Colleagues at the University of Groningen, Jacobs University and Klompenfabriek, thank you for the good times, the interesting discussions, and for letting me blow off steam! I truly enjoyed the lunch and coffee breaks, the vrijmibo's, the beerloquia, and other social events. In particular, I would like to thank my roommates Hanneke, Agnes, Ludger, Tjerk, Lea, Jaco, Ingrid, Ralf, Suzanne, and Leonieke. Jaco and Ruben deserve a special note for helping me with some of the graphics and Menno for reviewing the Dutch summary. Most closely I worked together with Lena in Bremen. Lena, I admire your passion, perseverance, and positive energy. Thank you for your amazing organization skills, making sure everything was running perfectly despite the complexity and extent of the project.

Many people outside of work supported me in these exciting but challenging times. First of all, I would like to thank my parents for their unconditional love and support, and for being my tower of strength. I would also like to thank my old housemates in Boschlust, who felt like a second family to me. This special, warm, and open group of people has inspired me and changed my way

of thinking in many ways. Besides Boschlust, several other close friends have supported me by listening, distracting and helping me to relax. In particular I would like to mention Anke, Joeri, Jos, Adrian, Brenda, Wendy, Sabine, Frank, and all my Ultimate Frisbee teammates. Ulf and Brenda, I owe you special thanks for the many times I could sleep over at your places and making me feel at home.

Anke and Ulf, thanks for agreeing to being my paranymphs! Anke, you invited me over for diner on my very first night in Groningen and we have remained friends ever since. I always enjoy being in your company, that is both relaxing and refreshing. Ulf, you may be the most social person that I know, which is why it is never boring to be around you. In any case, you are the person that got closest to unite the different disciplines on the second floor. I trust you will continue this effort when I'm gone.

Dearest Jeroen, thank you so much for being there for me. Your love and trust was what kept me standing during the difficult times. Sometimes I feel like you know me better than I know myself, always giving me exactly what I need. I am so glad we found each other and I hope we will have a long and happy future together.

ABOUT THE AUTHOR

Selma Papegaaij was born on August 21st 1986 in Kampen, the Netherlands. In 2004 she graduated from secondary school at the Almere College in Kampen. After she finished her study Physiotherapy at the Hanze University of Applied Sciences in Groningen in 2008, she continued her education and received a master's degree with the distinction *cum laude* in Human Movement Sciences from the University of Groningen in 2011. During her studies she worked as a physiotherapist at a private practice specialized in chronic diseases and was active in many committees at her sports clubs. Her master's project was conducted at the balance disorders laboratory at the Oregon Health & Science University in Portland under supervision of Prof. dr. F. Horak and Prof. dr. E. Otten.

Immediately after obtaining her master's degree, Selma started her PhD research in Human Movement Sciences at the University of Groningen with Prof. T. Hortobágyi as promotor and main supervisor. Her work focused on the age-related changes in neural control of posture, using electrophysiological techniques such as transcranial magnetic stimulation and peripheral nerve stimulation. She also stayed six months in Bremen, to conduct a functional magnetic resonance imaging study on dual-tasking under supervision of Prof. dr. C. Voelcker-Rehage.

During her PhD, Selma received a young investigator award from the European College of Sport Science and the second prize for her presentation at the Graduate School of Medical Sciences poster afternoon. Also, she received a grant from the Gratama Stichting to finance her study in Bremen.

Selma is currently looking to continue her career in human movement science, unraveling the mysteries of motor control and learning.

PUBLICATIONS

Papegaaij S., Taube W., van Keeken H.G., Otten E., Baudry S., Hortobágyi T. Young and old adults downmodulate intracortical inhibition when postural challenge is high. Experimental Gerontology, 73: 78-85, 2016.

Papegaaij S., Taube W., Hogenhout M., Baudry S., Hortobágyi T. Age-related decrease in motor cortical inhibition during standing under different sensory conditions. Frontiers in Aging Neuroscience, 126(6): 2014.

Papegaaij S., Taube W., Baudry S., Otten E., Hortobágyi T. Aging causes a reorganization of cortical and spinal control of posture. Frontiers in Aging Neuroscience, 28(6): 2014.

Papegaaij S., de Lima-Pardini A.C., Smith B.A., Otten E., Cohen R.G., Horak F.B. Keeping your balance while balancing a cylinder: interaction between postural and voluntary goals. Experimental Brain Research, 223(1):79-87, 2012.

de Lima-Pardini A.C., **Papegaaij S.**, Cohen R.G., Teixeira L.A., Smith B.A., Horak F.B. The Interaction of Postural and Voluntary Strategies for Stability in Parkinson's Disease. Journal of Neurophysiology, 108(5):1244-52, 2012.

SUBMITTED FOR PUBLICATION

Papegaaij S., Baudry S., Négyesi J., Taube W., Hortobágyi T. Intracortical inhibition in the soleus muscle is reduced during the control of upright standing in both young and old adults.

Papegaaij S., Hortobágyi T., Godde B., Kaan W.A., Erhard P., Voelcker-Rehage C., Neural correlates of motor-cognitive dual-tasking in young and old adults.

CONFERENCE PROCEEDINGS

Papegaaij S., Hortobágyi T., Godde B., Erhard P., Voelcker-Rehage C. (2015). Neural correlates of dual-tasking in young and old adults. Society for Neuroscience Annual Meeting. Chicago.

Papegaaij S., Taube W., van Keeken H.G., Otten E., Baudry S., Hortobágyi T. (2015). Different motor cortical processing between voluntary and postural tasks in both young and old adults. International Society for Gait and Posture Research World Congress. Sevilla.

Papegaaij, S., Taube, W., Baudry, S., Négyesi, J., Hortobágyi, T. (2014). Intracortical inhibition is reduced during the control of upright standing in both young and old adults. Society for Neuroscience Annual Meeting. Washington D.C.

Papegaaij S., Taube W., Hogenhout M., Baudry S., Hortobágyi T. (2014) Different modulation of motor cortical inhibition between postural tasks in young and old adults. Japanese Society of Physical Fitness and Sports Medicine Annual Congress (JSPFSM-ECSS exchange). Nagasaki.

Papegaaij S., Taube W., Hogenhout M., Baudry S., Hortobágyi T. (2014) Different modulation of motor cortical inhibition between postural tasks in young and old adults. European College of Sport Science Annual Congress. Amsterdam.

Papegaaij, S., Taube, W., Hogenhout, M., Baudry, S., Hortobágyi, T. (2014). Age-related decrease in motor cortical inhibition during different postural tasks. Neural Control of Movement Annual Meeting.